Acute Renal Allograft Dysfunction

Hussein Sheashaa, MD, FACP

Professor of Nephrology, Urology and Nephrology Center and Director of Medical E-Learning Unit, Mansoura University, and Executive Director of ESNT- Virtual Academy:
http://lms.mans.edu.eg/esnt/

MNDU, March 18th, 2016

Urology and Nephrology Center

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DNG
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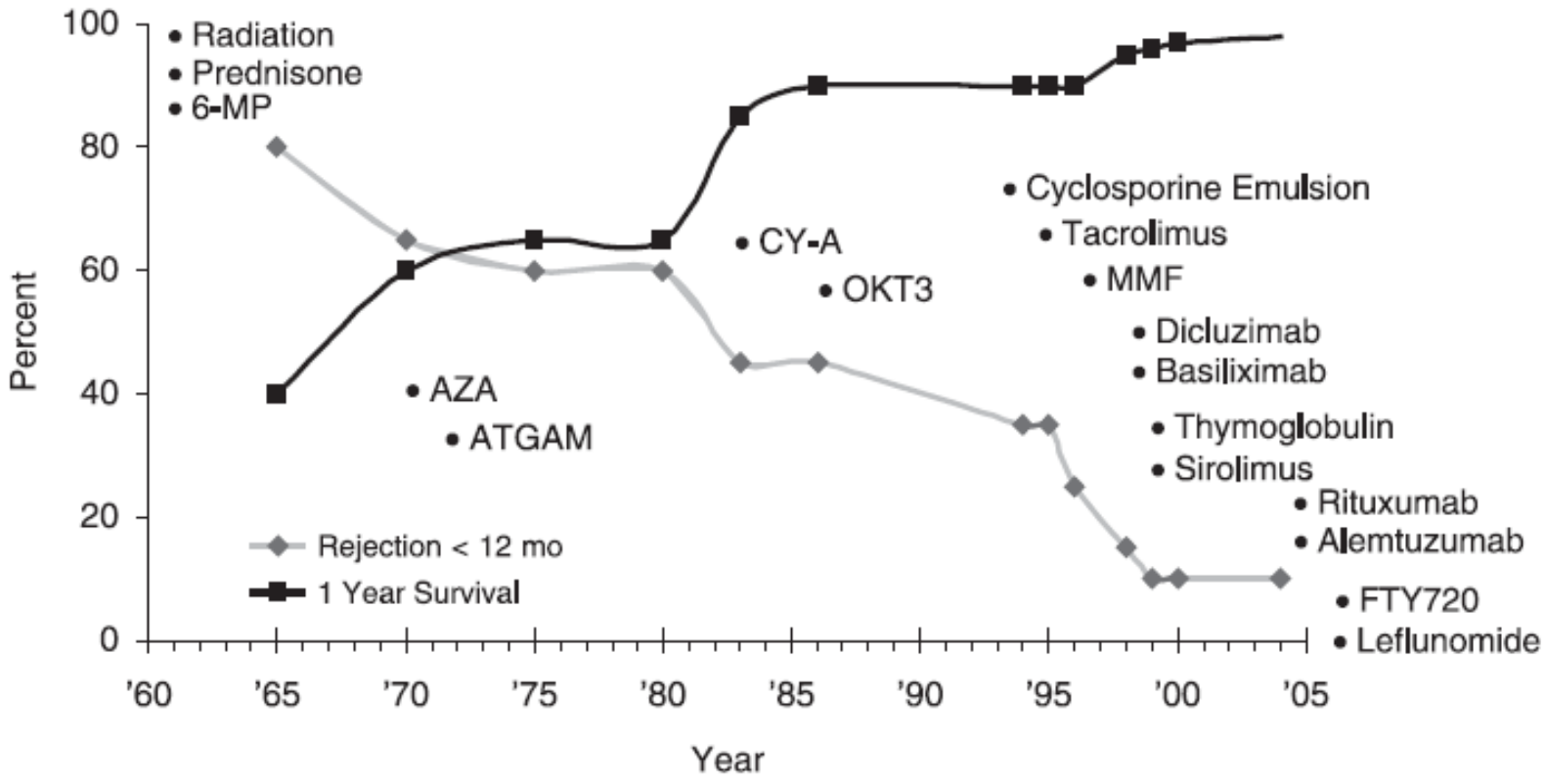
رابطة أطباء الكلى بالمنصورة

Urology and Nephrology Center

Corners

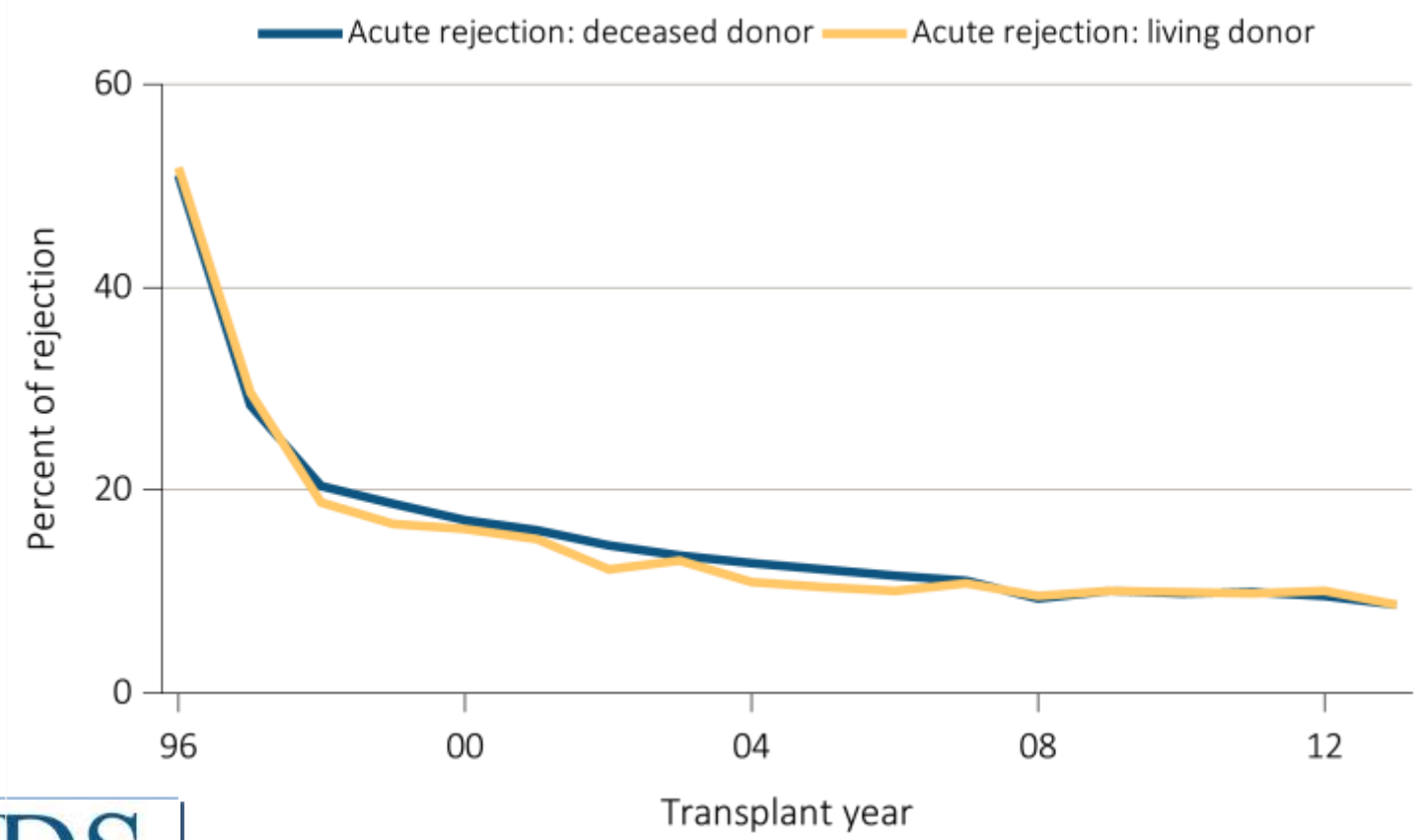
1. Introduction
2. Acute cellular rejection
3. Acute antibody mediated rejection
4. Warm ischemia
5. CNI nephrotoxicity
6. Infection
7. Graft rupture
8. Pre-renal and intrinsic renal
9. Closure

Evolution of Immunosuppressive Drugs and Rejection



Zand. *Seminars in Dialysis 2005; 18 (6): 511-519*

Acute Rejection:
Within The First Year



USRDS
UNITED STATES RENAL DATA SYSTEM

December, 2015

Hindawi Publishing Corporation
BioMed Research International
Volume 2013, Article ID 912413, 9 pages
http://dx.doi.org/10.1155/2013/912413

Research Article

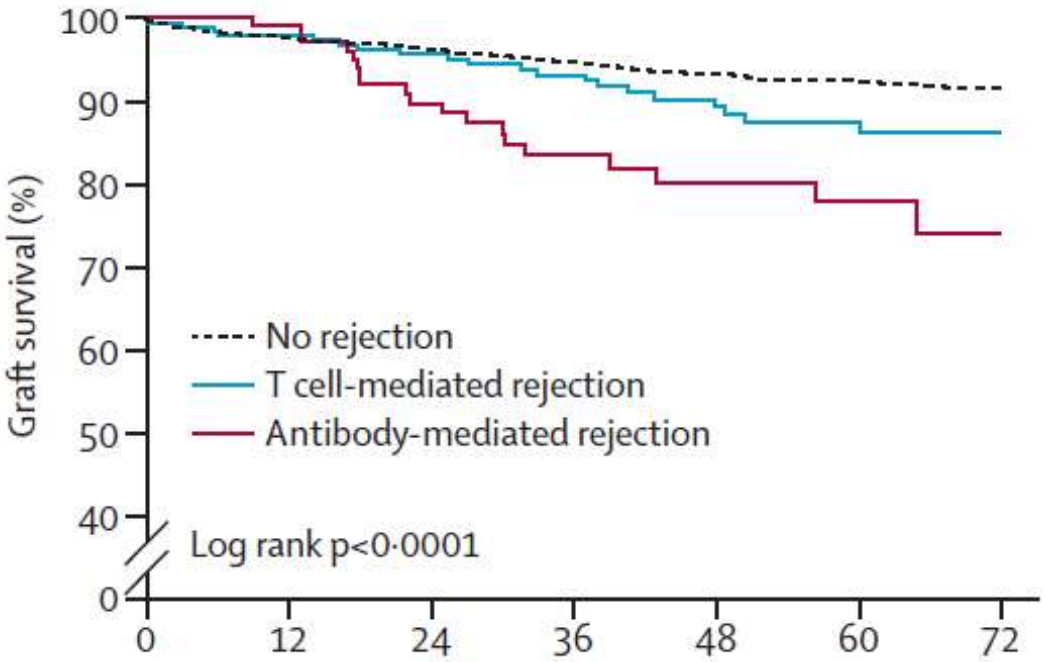
Factors Affecting Graft Survival among Patients Receiving Kidneys from Live Donors: A Single-Center Experience

Mohamed A. Ghoneim,[1] Mohamed A. Bakr,[2] Ayman F. Refaie,[2] Ahmed I. Akl,[2] Ahmed A. Shokeir,[1] Ahmed B. Shehab El-Dein,[1] Hesham M. Ammar,[2] Amani M. Ismail,[3] Hussein A. Sheashaa,[2] and Mahmoud A. El-Baz[4]

[1] *Department of Urology, The Urology & Nephrology Center, Mansoura, Egypt*
[2] *Division of Nephrology, The Urology & Nephrology Center, Mansoura, Egypt*
[3] *Division of Immunology, The Urology & Nephrology Center, Mansoura, Egypt*
[4] *Division of Pathology, The Urology & Nephrology Center, Mansoura, Egypt*

	No. of patients	5-year survival %	95% CI		10-year survival %	95% CI		*P* value (log rank)
No. of acute rejection episodes (during first 3 months)								
(i) No	708	94.2	92.44	95.96	82.1	78.18	86.02	
(ii) One	661	89.6	87.25	91.95	69.4	65.28	73.52	**<0.001**
(iii) ≥2	598	75.8	72.27	79.33	47.5	43.19	51.81	

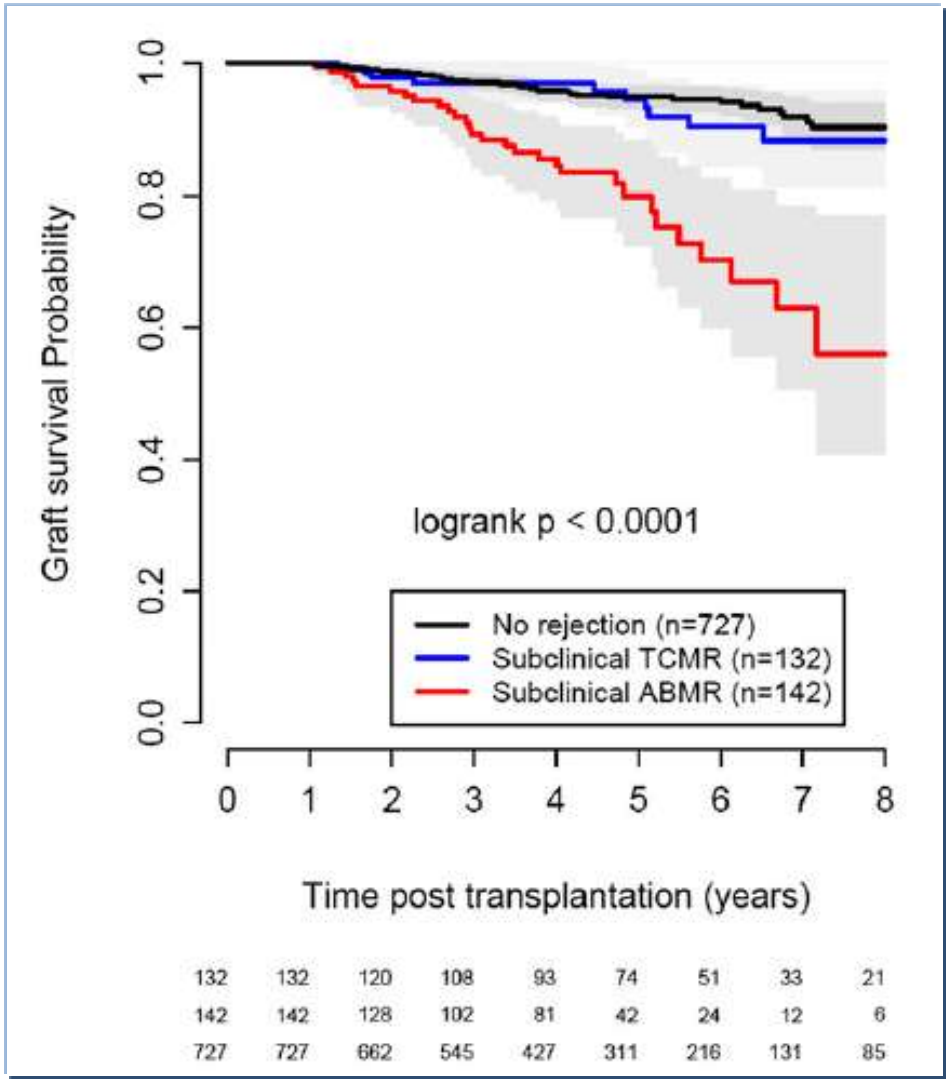
Impact of Rejection



Number at risk							
No rejection	1777	1600	1408	1152	933	673	473
T cell-mediated rejection	192	182	163	134	101	71	37
Antibody-mediated rejection	110	100	78	61	40	26	12

Lefaucheur, et al. ***Lancet* 2013; 381: 313–19**

Impact of Rejection



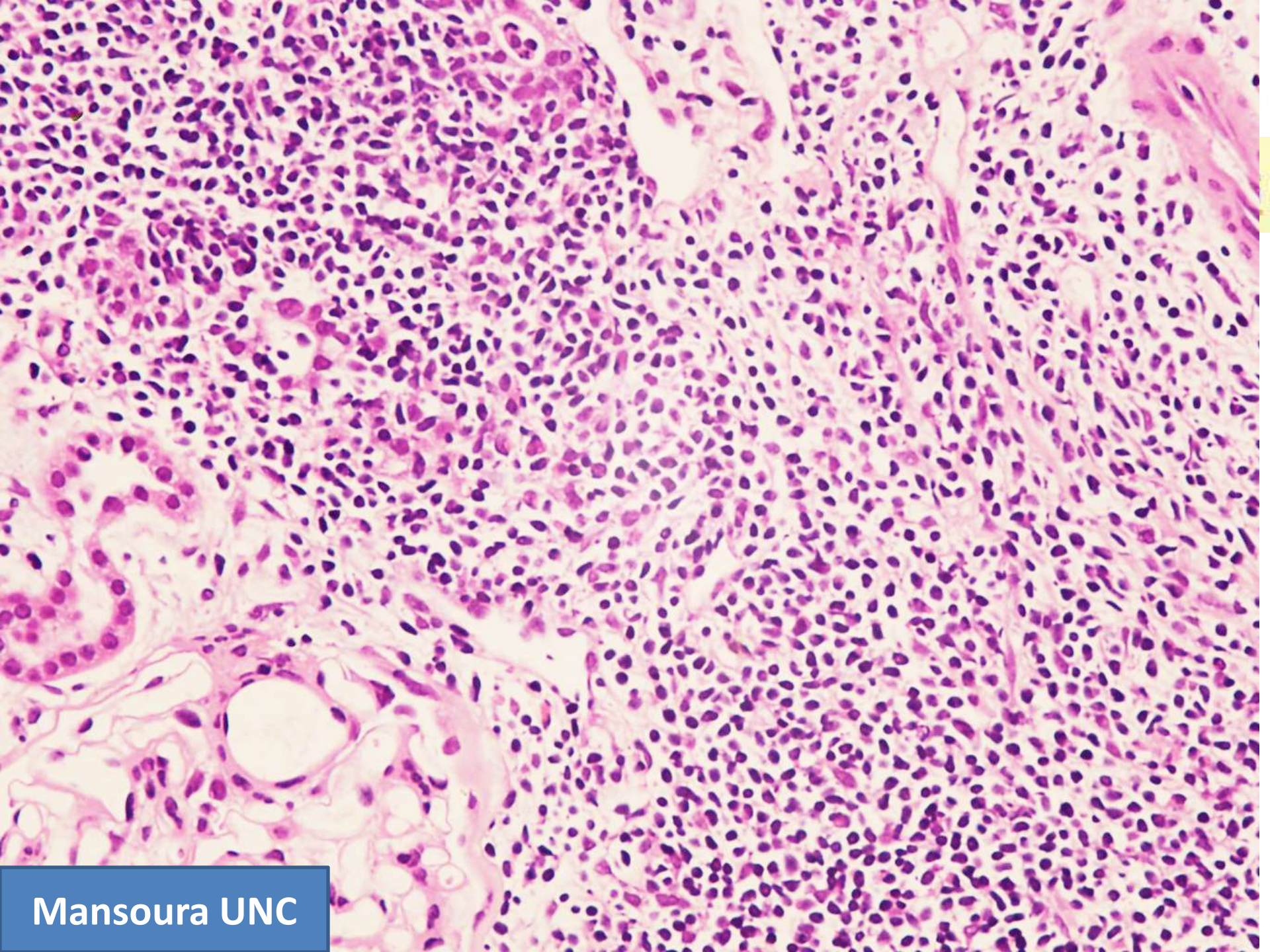
J Am Soc Nephrol 26: 1721–1731, 2015

Diagnosis of Rejection: Adequate Biopsy

- 2 cores of cortex or 2 separate cortical areas.
- Adequate: > 10 glomeruli and > 2 arteries
- Minimal : 7 glomeruli and 1 artery
- Slide preparation: 7 slides (multiple sequential sections.
  - Hematoxylin and eosin (HE): 3 slides
  - Periodic acid –Schiff (PAS) or silver: 3 slides
  - Trichrome: 1 slide

The Banff Schema

Acute Cellular Rejection



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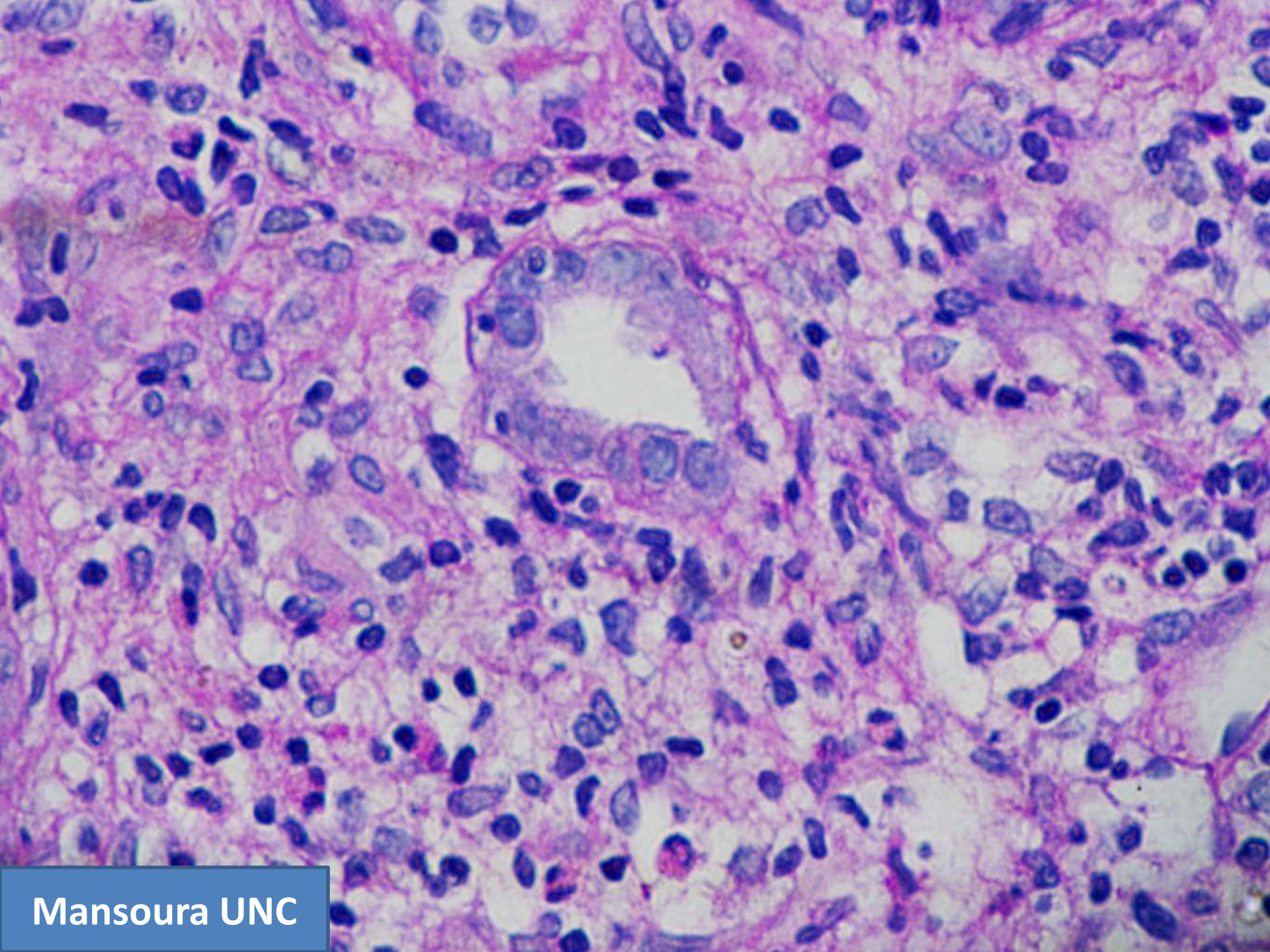
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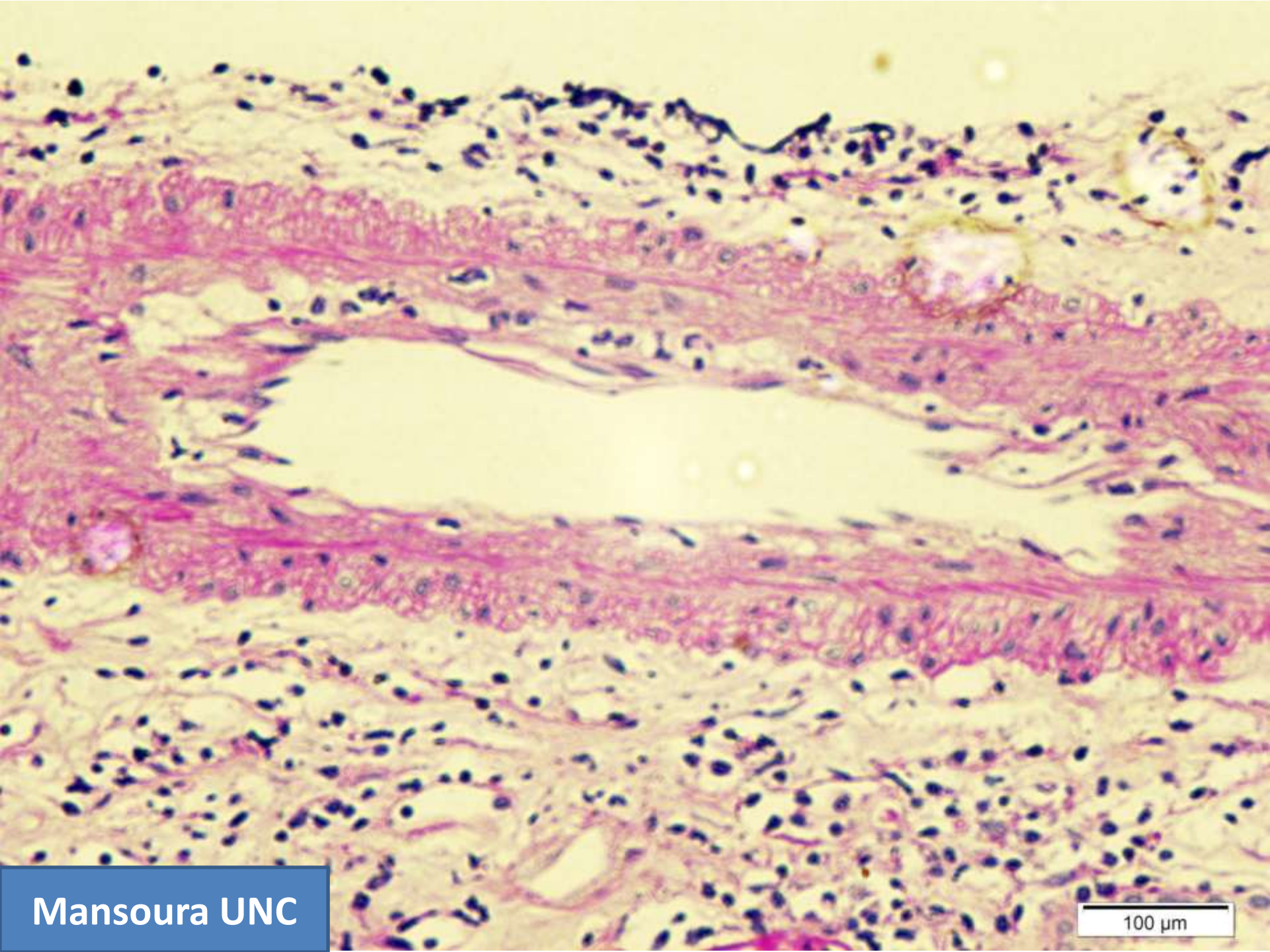

Mansoura UNC
100 µm

Acute Cellular Rejection: Banff 2009 Schema

3. Borderline changes: 'Suspicious' for acute T-cell mediated rejection
   This category is used when no intimal arteritis is present, but there are foci of tubulitis (t1, t2 or t3) with minor interstitial infiltration (i0 or i1) or interstitial infiltration (i2, i3) with mild (t1) tubulitis
4. T-cell mediated rejection

Acute T-cell mediated rejection (Type/Grade:)

- IA. Cases with significant interstitial infiltration (>25% of parenchyma affected, i2 or i3) and foci of moderate tubulitis (t2)
- IB. Cases with significant interstitial infiltration (>25% of parenchyma affected, i2 or i3) and foci of severe tubulitis (t3)
- IIA. Cases with mild to moderate intimal arteritis (v1)
- IIB. Cases with severe intimal arteritis comprising >25% of the luminal area (v2)
- III. Cases with 'transmural' arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle cells with accompanying lymphocytic inflammation (v3)

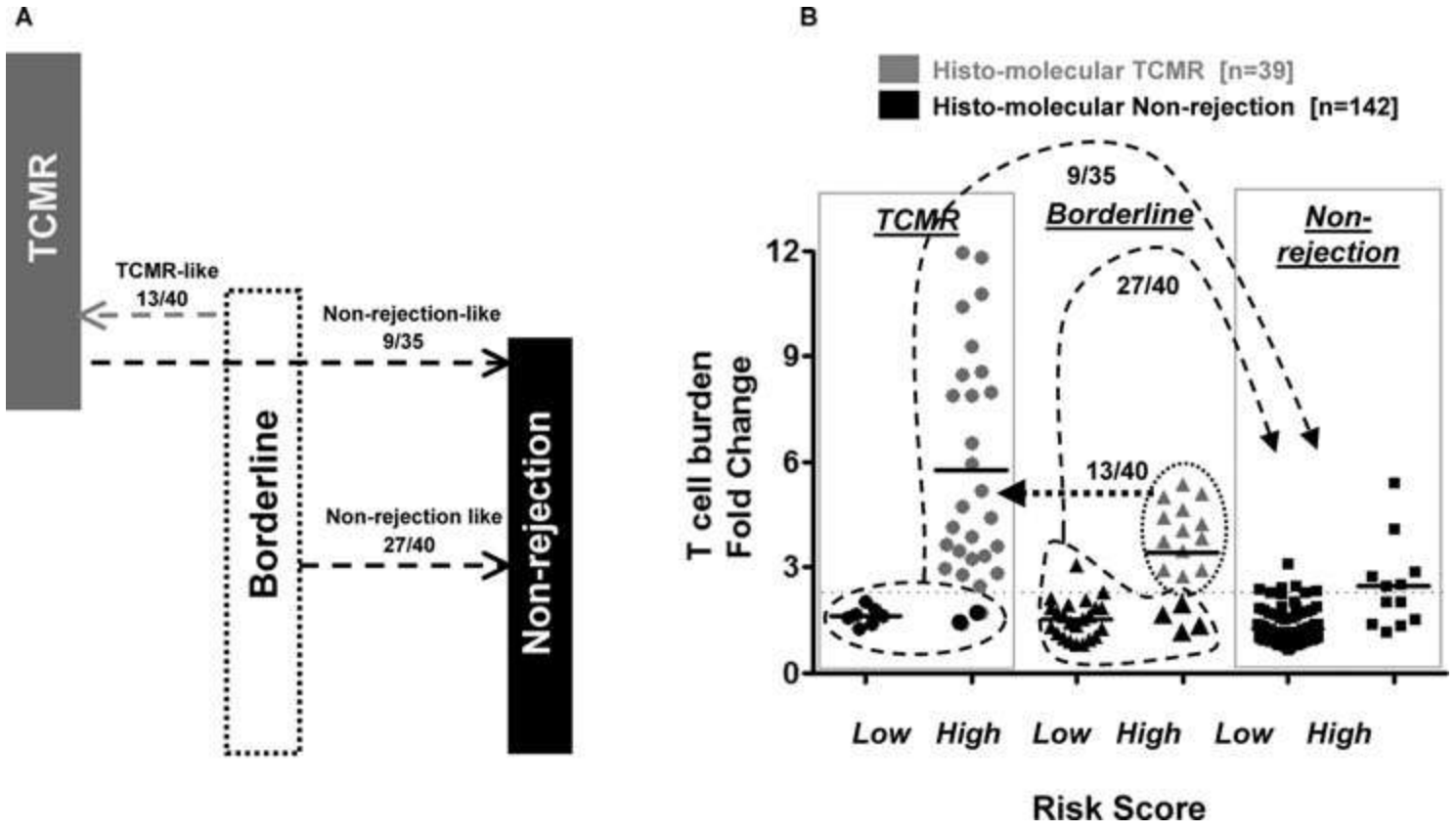
Sis, et al. Am J Transplant 2010; 10: 464-471.

Acute Cellular Rejection: Classifications

- **Time**:
  - Early or late (before or after 6 months)
- **Type:**
  - Borderline changes: Low severity
  - TCMR I (interstitial rejection): Moderate severity
  - TCMR II/III (vascular rejection): High severity
- **Response:**
  - Complete
  - Partial reversibility :(serum creatinine > 25%-< 75% of basal creatinine
  - No reversibility: serum creatinine > 75% of basal creatinine

Wu et al. Transplantation 2014;97: 1146-1154

Reclassifying Borderline to TCMR or Nonrejection



de Freitasa, et al. *American Journal of Transplantation 2012; 12: 191–201*

Late Acute Cellular Rejection (after 90 days): 355 episodes in a cohort of 5758 patients

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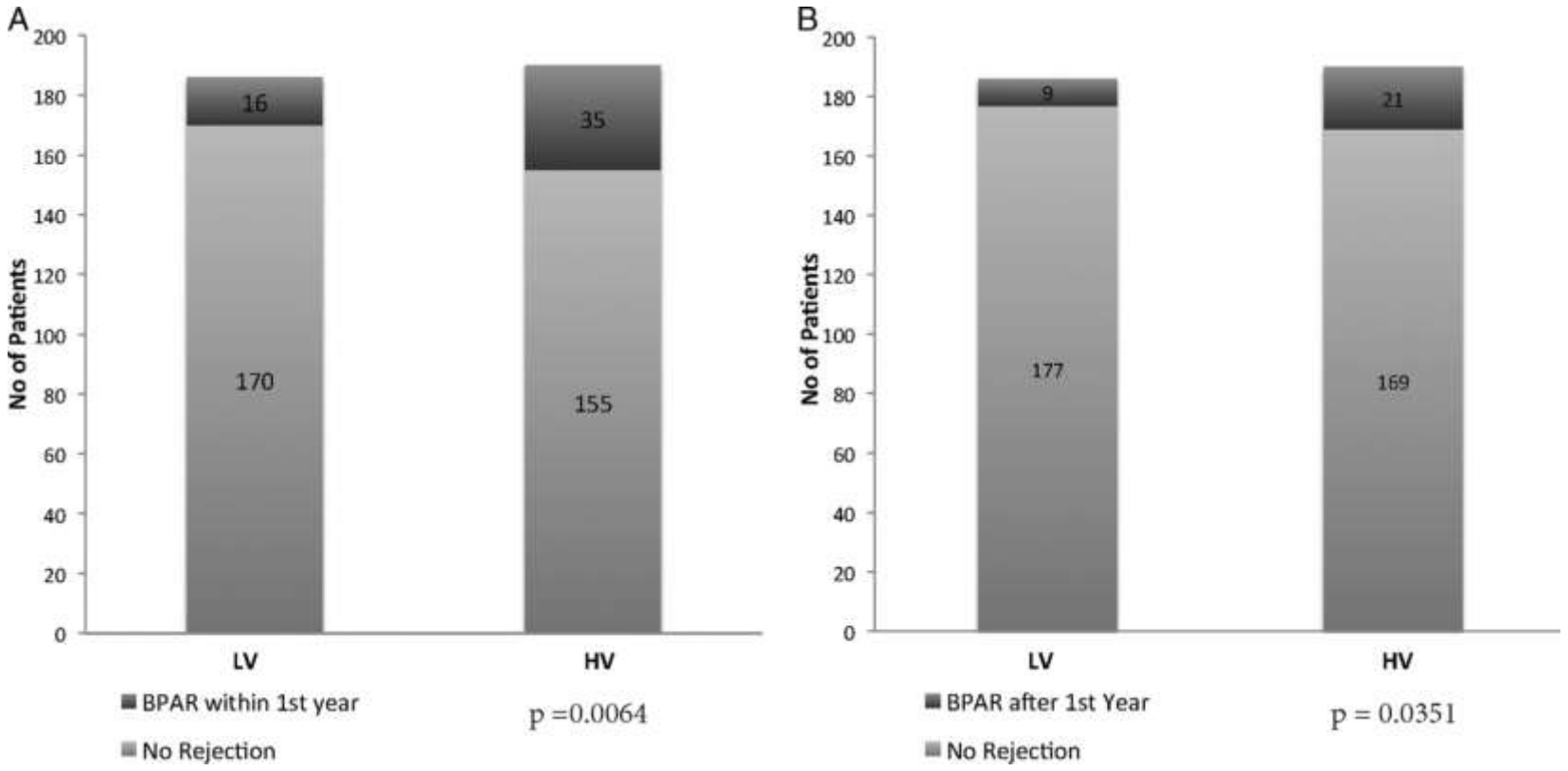
CLINICAL AND TRANSLATIONAL RESEARCH

Clinicopathological Characteristics and Effect of Late Acute Rejection on Renal Transplant Outcomes

A total of 215 patients had 1 episode, 57 had 2 episodes, and 13 had 3 episodes of LAR.

Rodrigues et al. Transplantation 2014 May 12

Resistant Acute Rejection:
Tacrolimus Variability



Transplantation 2016; in press

Predictors of Acute Cellular Rejection: Salt Intake

BRIEF COMMUNICATION www.jasn.org

Salt Accelerates Allograft Rejection through Serum- and Glucocorticoid-Regulated Kinase-1–Dependent Inhibition of Regulatory T Cells

Kassem Safa,*† Shunsuke Ohori,* Thiago J. Borges,*‡ Mayuko Uehara,* Ibrahim Batal,§ Tetsunosuke Shimizu,* Ciara N. Magee,*‖ Roger Belizaire,§ Reza Abdi,* Chuan Wu,¶ Anil Chandraker,* and Leonardo V. Riella*

*Schuster Family Transplantation Research Center, Renal Division, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; †Transplant Center and Division of Nephrology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; ‡School of Biosciences and Biomedical Research Institute, Pontifical Catholic University of Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brazil; §Department of Pathology, Brigham and Women's Hospital, Boston, Massachusetts; ‖Department of Renal Medicine and Transplantation, Royal Free London, National Health Service Foundation Trust, London, United Kingdom; and ¶Center for Neurologic Diseases, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

J Am Soc Nephrol 26: 2341–2347, 2015

Resistant Acute Rejection:

CD4+ CD28-

American Journal of Transplantation 2016; XX: 1–2
Wiley Periodicals Inc.

Editorial

Belatacept resistance and T cells

Category	Phenotype	Setting	Other characteristic
CD4+	PD-1-CD57+CD28–	Prior to kidney transplant. Possible prediction of recipients who may develop costimulation blockade-resistant rejection (CoBRR)	Highly express adhesion molecules (CD2, LFA1, VLA4); cytotoxic enzymes (Granzyme B); pro-inflammatory cytokines (interferon γ [IFN-γ], tumor necrosis factor α [TNF-α)
	Th17 (CD28+)	Kidney transplant recipients with CoBRR	Correlated with CoBRR; resistant to belatacept inhibition
	Treg	Mouse MHC class-II mismatched cardiac transplant model	Deleterious effect on thymic-derived Tregs
CD8+	CD28–	Healthy volunteers (*in vitro* experiments)	IL-15-dependent; produce high amounts of IFN-γ, TN-α; +CD107a in proliferating cells

Treatment of Acute Rejection: KDIGO Guidelines

6.1: We recommend biopsy before treating acute rejection, unless the biopsy will substantially delay treatment. *(1C)*

6.2: We suggest treating subclinical and borderline acute rejection. *(2D)*

6.3: We recommend corticosteroids for the initial treatment of acute cellular rejection. *(1D)*

6.3.1: We suggest adding or restoring maintenance prednisone in patients not on steroids who have a rejection episode. *(2D)*

6.3.2: We suggest using lymphocyte-depleting antibodies or OKT3 for acute cellular rejections that do not respond to corticosteroids, and for recurrent acute cellular rejections. *(2C)*

American Journal *of* Transplantation 2009, Volume 9, suppl 3

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2

Acute Antibody Mediated Rejection

Mechanism of Acute AMR

REVIEW

CURRENT OPINION

Mechanisms of antibody-mediated acute and chronic rejection of kidney allografts

William M. Baldwin III[a,b], *Anna Valujskikh*[a,b], *and Robert L. Fairchild*[a,b]

Curr Opin Organ Transplant 2016, 21:7–14

Mechanism of Acute AMR

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Antibody mediated rejection in sensitized non-human primates: modeling human biology

Christopher K. Burghuber[1,2], Jean Kwun[1,3], Eugenia J Page[1], Miriam Manook[3], Adriana C Gibby[1], Frank V Leopardi[1,3], Minqing Song[1,3], Alton B Farris III[4], Jung Joo Hong[4,5,6], Francois Villinger[4,5], Andrew B. Adams[1], Neal N Iwakoshi[1] and Stuart J Knechtle[1,3,*]

[1] Emory Transplant Center, Department of Surgery, Emory School of Medicine, Atlanta, Georgia

American Journal of Transplantation, 2016, Accepted article

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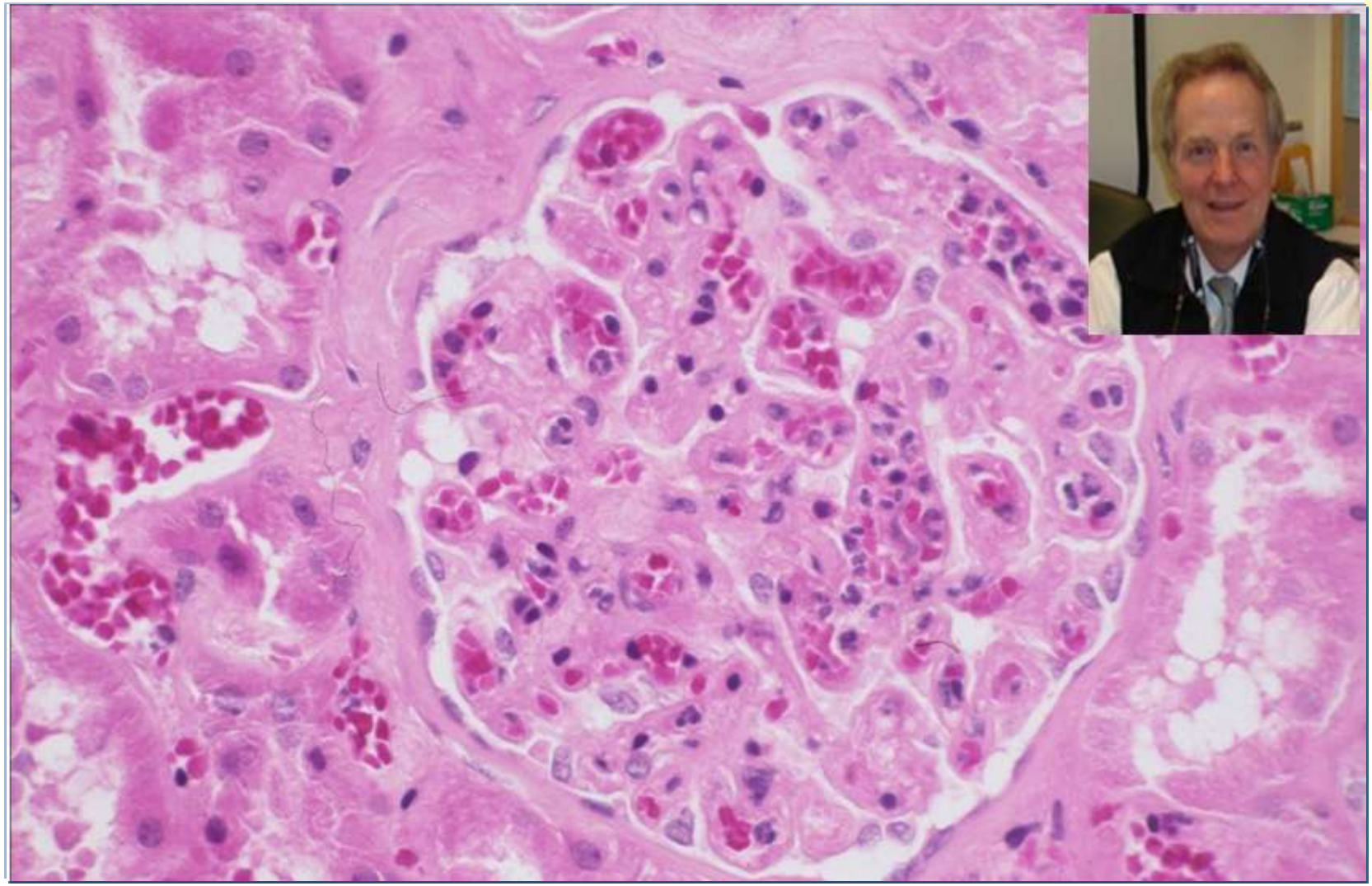
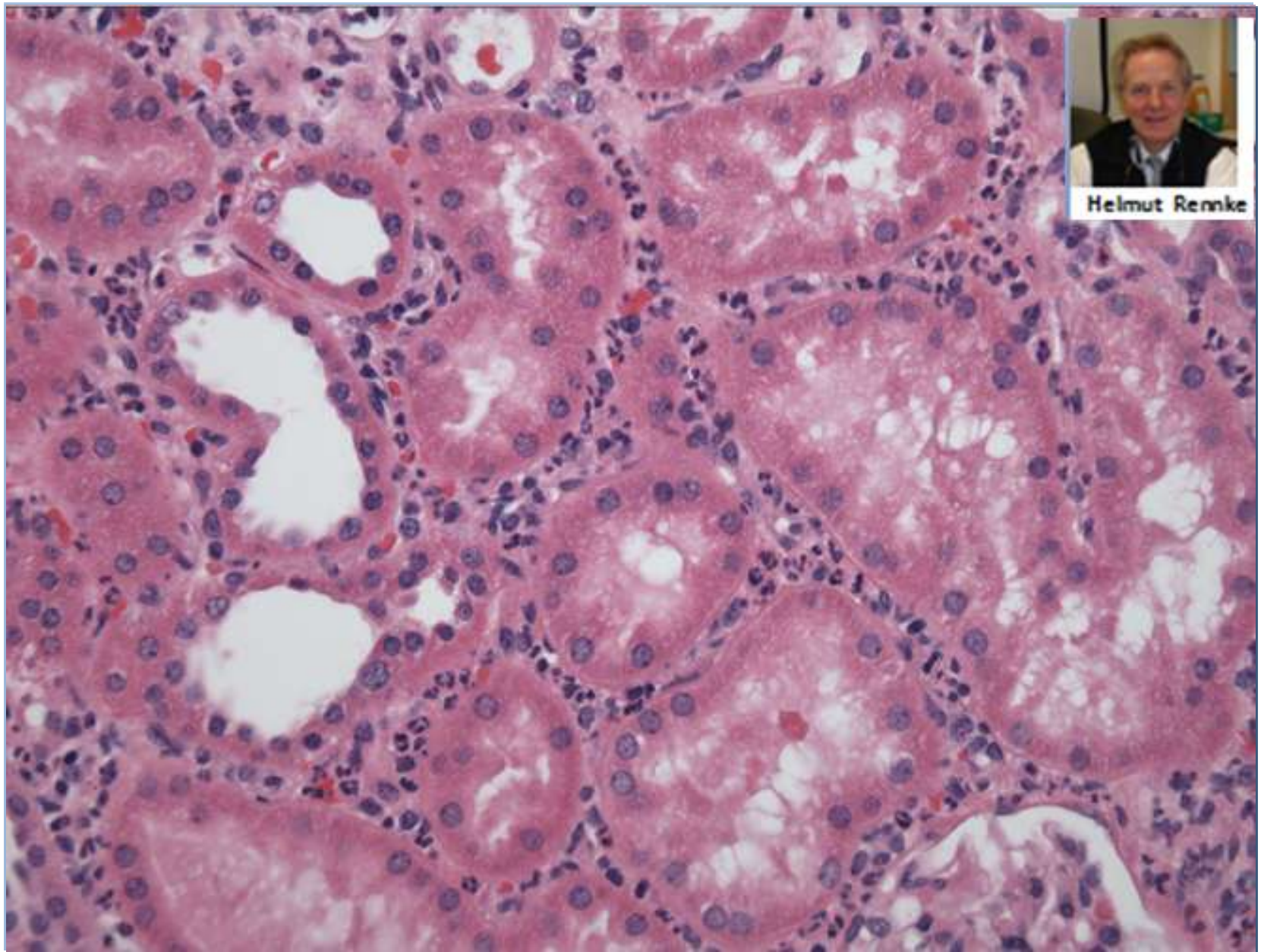


g: glomerulitis

- g0= No glomerulitis
- g1= glomerulitis in less than 25% of glomeruli
- g2= segmental or global glomerulitis in 25 to 75% of glomeruli
- g3= glomerulitis (mostly global) in more than 75% of glomeruli

The Banff 97 working clas. . Kidney Int 1999; 55: 713–723.

ptc



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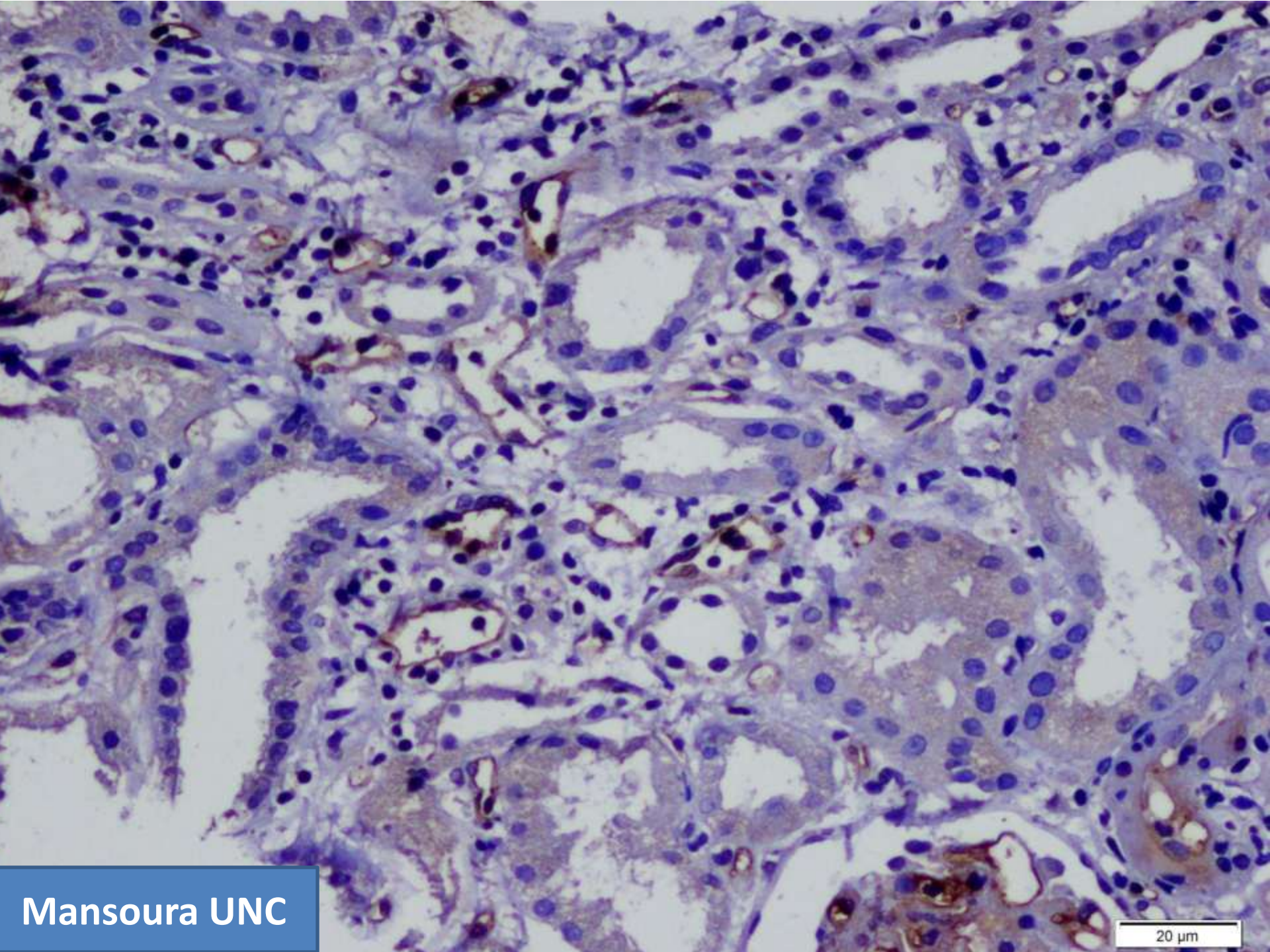
Mansoura UNC
20 µm

Urology and Nephrology Center

Helmut Remmke

c4d0

c4d3

American Journal of Transplantation 2016; XX: 1–6
Wiley Periodicals Inc.

Minireview

The Revised (2013) Banff Classification for Antibody-Mediated Rejection of Renal Allografts: Update, Difficulties, and Future Considerations

M. Haas*

Department of Pathology and Laboratory Medicine, Cedars-Sinai Medical Center, Los Angeles, CA

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Banff 2013 classification of ABMR in renal allografts, simplified

Acute/active ABMR: *All three features must be present for diagnosis*[1]

1. Histologic evidence of acute tissue injury, including one or more of the following:
   MVI (glomerulitis [g > 0] if no glomulonephritis, and/or peritubular capillaritis [ptc > 0]; **g > 0 must be present if there is concurrent TCMR/borderline**)
   Intimal or transmural arteritis (v > 0)
   Acute TMA without other cause
   Acute tubular injury without other cause
2. **Evidence of current or recent antibody interaction with vascular endothelium, including at least one of the following:**
   Linear C4d staining in peritubular capillaries[2]
   At least moderate MVI ([g + ptc] ≥2), with the same qualifiers as above
   Molecular markers, if properly validated
3. Serologic evidence of donor-specific antibodies (HLA or other antigens)

Diagnosis of AMR:

Value of C4d

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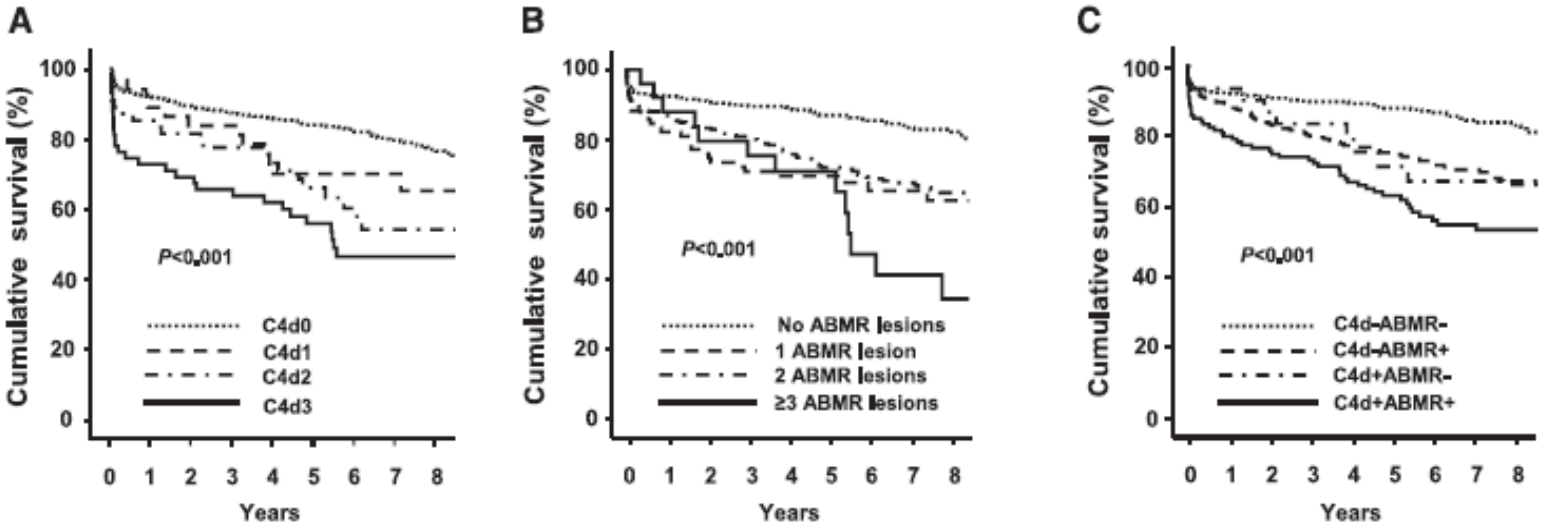
Capillary C4d and Kidney Allograft Outcome in Relation to Morphologic Lesions Suggestive of Antibody-Mediated Rejection



Clin J Am Soc Nephrol 10: 1435–1443, 2015.

Strategies to Prevent AMR

1. Do not transplant highly sensitized patients
2. Avoid blood transfusion
3. Paired kidney exchange
4. In sensitized patients, precise characterization of their alloantibodies and exact HLA typing of the donor at the time of transplantation
5. Participation in special programs (such as the Eurotransplant Acceptable Mismatch Program)
6. Removal of DSA (plasmapheresis, immunoadsorption)
7. Direct or indirect inhibition of DSA production
   a. Anti-B cell agents (rituximab[1])
   b. Anti-plasma cell agents (proteasome inhibitors, e.g. bortezomib[1])
   c. Rabbit anti-human thymocyte immunoglobulins (e.g. thymoglobulin)?
   d. Costimulation blockade (e.g. belatacept)?
8. Inhibition of complement cascade (eculizumab[1])
9. Intravenous immunoglobulin[1]
   e. Neutralizing DSA: anti-idiotypic activity
   f. Inhibiting complement activation by binding C3b, C4b
   g. Inhibiting activation of macrophages, neutrophils by binding FcγRs
   h. Apoptosis of B cells (inhibits CD19 expression)
10. Splenectomy

ABMR, antibody-mediated rejection; DSA, donor-specific antibodies; FcγRs, Fc gamma.
[1]These drugs are used off-label in solid organ transplantations.

The ideal regimen for the prevention of ABMR in sensitized patients remains unknown.

Djamali et al American Journal of Transplantation 2014; 14: 255–271

Original Clinical Science

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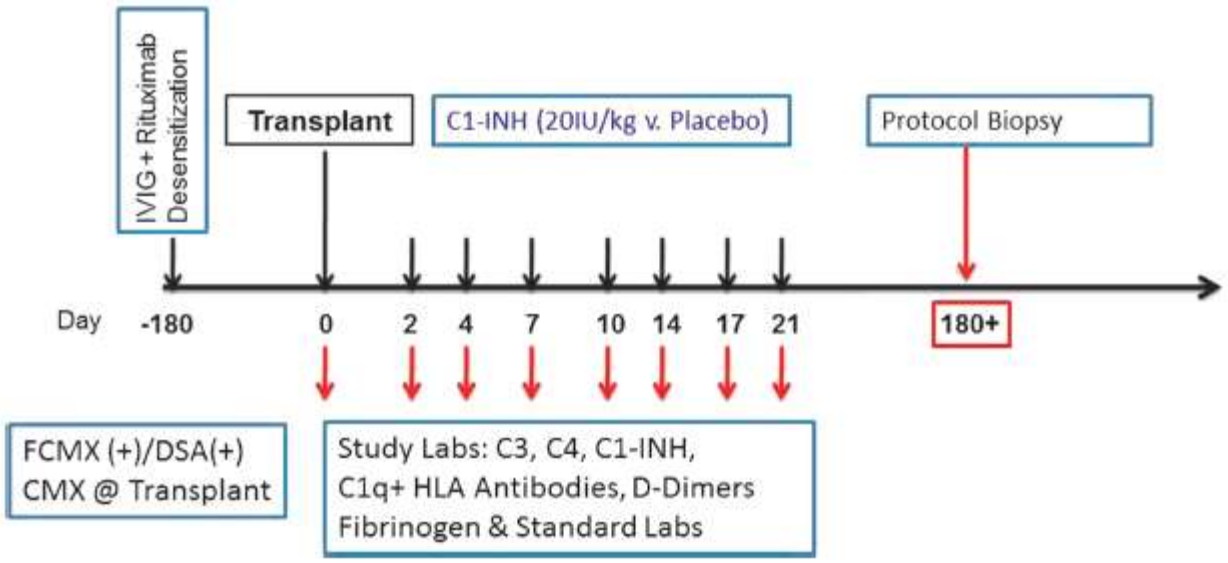
A Phase I/II Placebo-Controlled Trial of C1-Inhibitor for Prevention of Antibody-Mediated Rejection in HLA Sensitized Patients

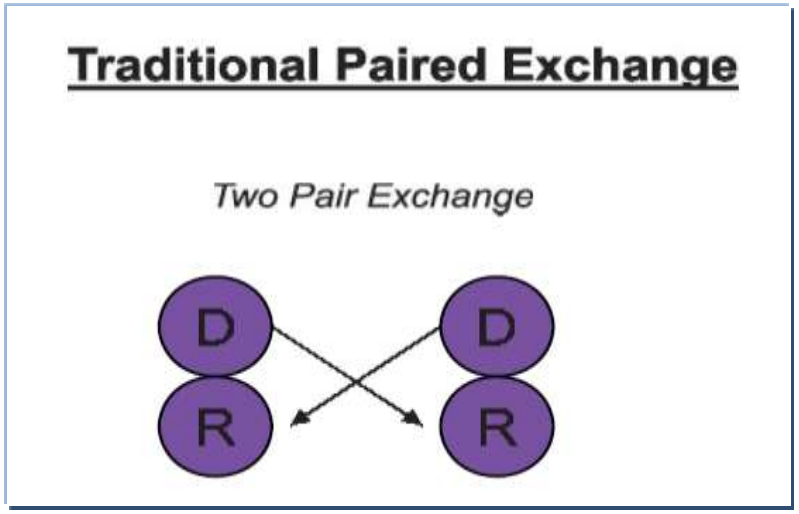
Ashley A. Vo,[1] Adriana Zeevi,[2] Jua Choi,[1] Kristen Cisneros,[1] Mieko Toyoda,[3] Joseph Kahwaji,[1] Alice Peng,[1] Rafael Villicana,[1] Dechu Puliyanda,[1] Nancy Reinsmoen,[4] Mark Haas,[5] and Stanley C. Jordan[1]

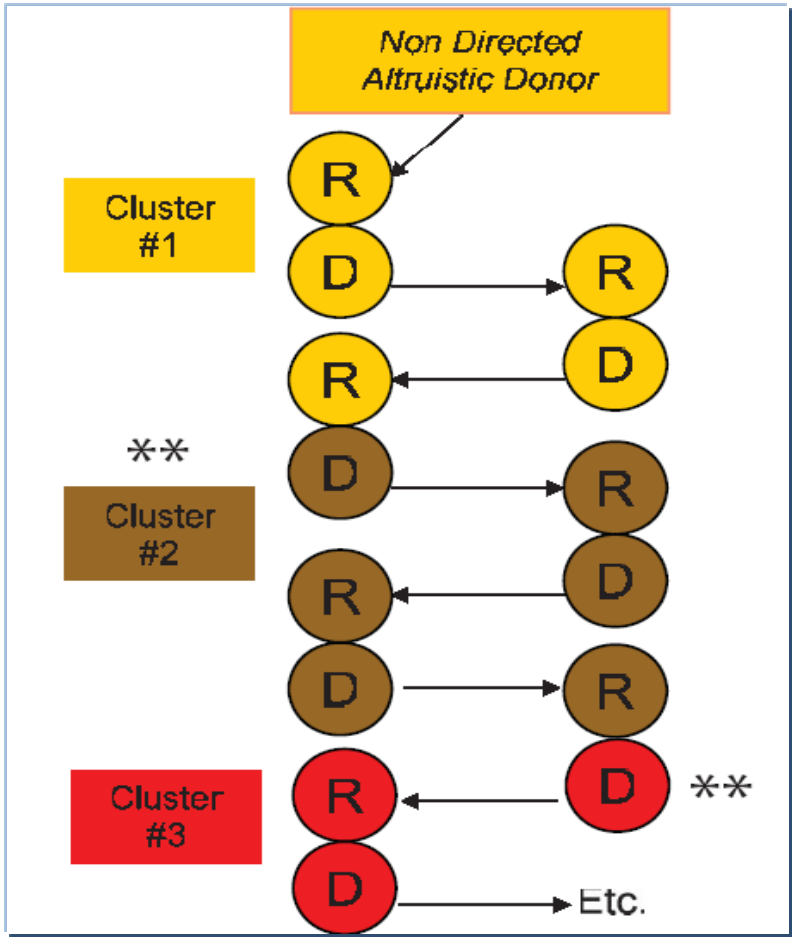
C1-INH Study Format



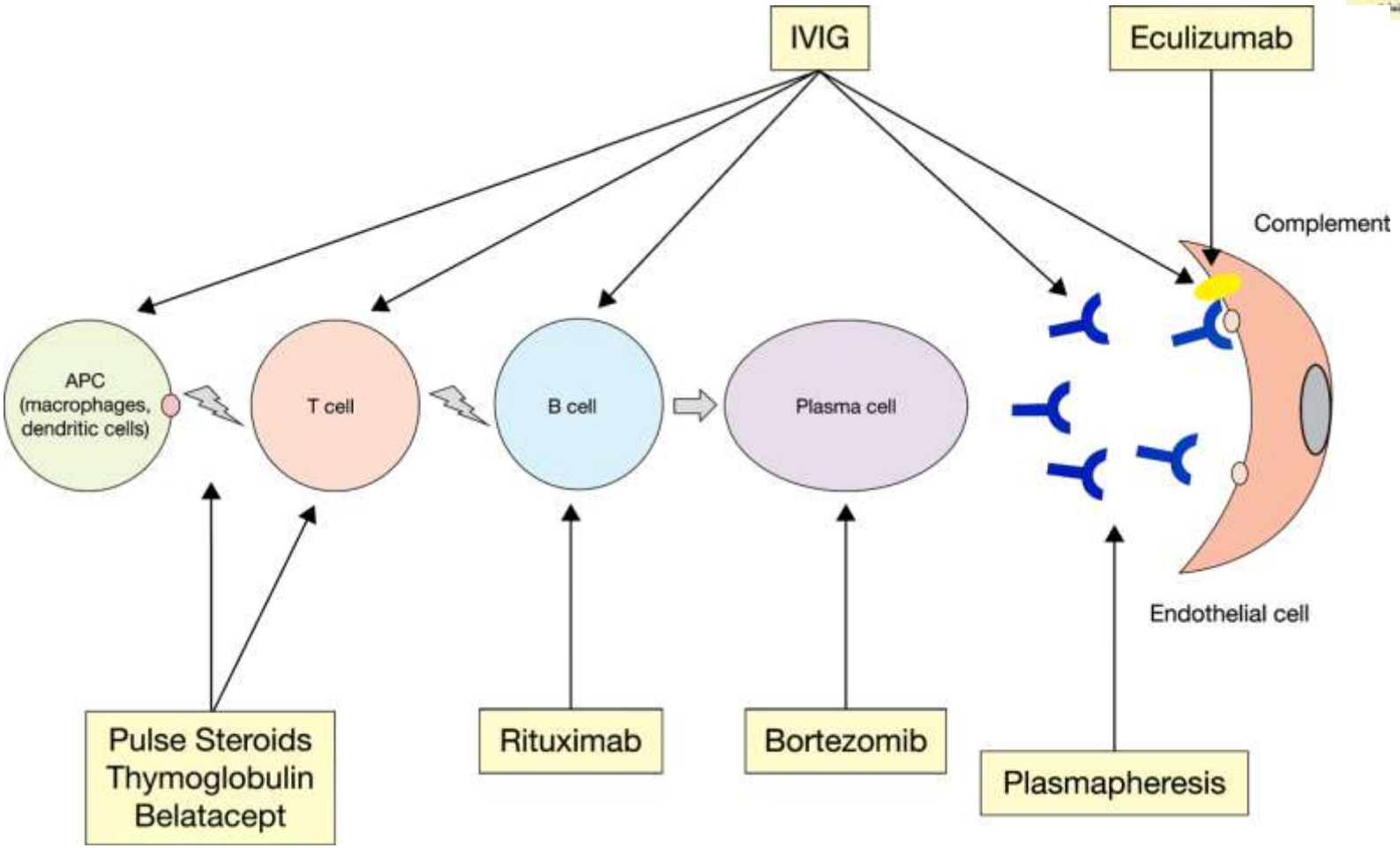
Transplantation Feb 2015;99: 299–308

Strategies to prevent AMR: Why Donor Exchange?





Treatment of Acute AMR



Djamali et al American Journal of Transplantation 2014; 14: 255–271

Acute Rejection:
AMR

REVIEW

CURRENT OPINION

Antibody-mediated rejection

Alessandro Amore

- Never forget that a humoral rejection is always associated with a cellular rejection.

Curr Opin Organ Transplant Oct 2015, 20:536–542

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3

Warm Ischemia

Kidney Injury:
Warm Ischemia

American Journal of Transplantation 2016; XX: 1–1
Wiley Periodicals Inc.

Letter to the Editor

Kidney Injury Due to Warm Ischemia During Transplantation Can Be Reduced

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4

CNI Nephrotoxicity

CNI Nephrotoxicity

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Review

The safety of calcineurin inhibitors for kidney-transplant patients

Paolo Malvezzi & Lionel Rostaing†

†*Department of Nephrology and Organ Transplantation, CHU Rangueil, Toulouse, France*

Published online: 02 Sep 2015.

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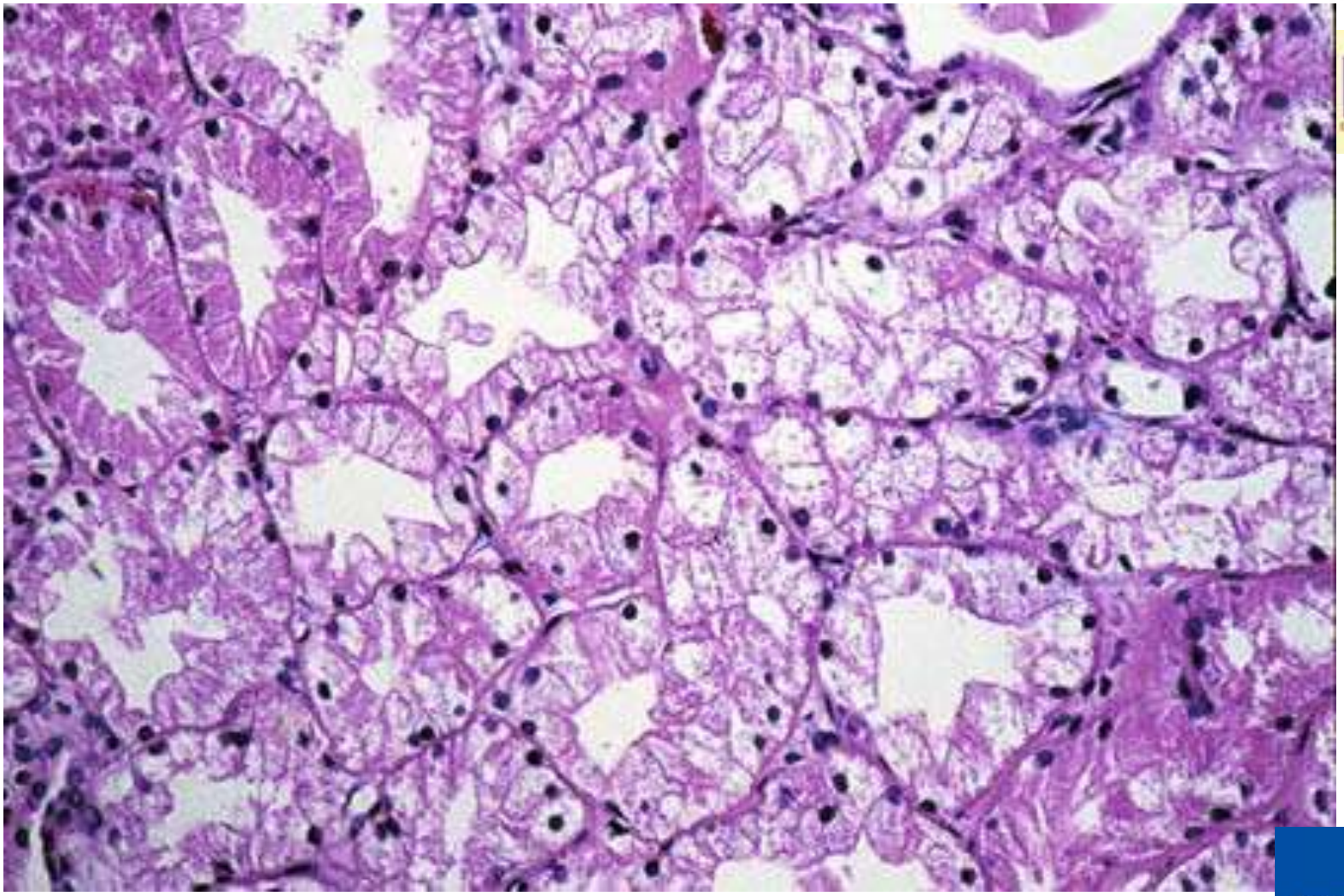

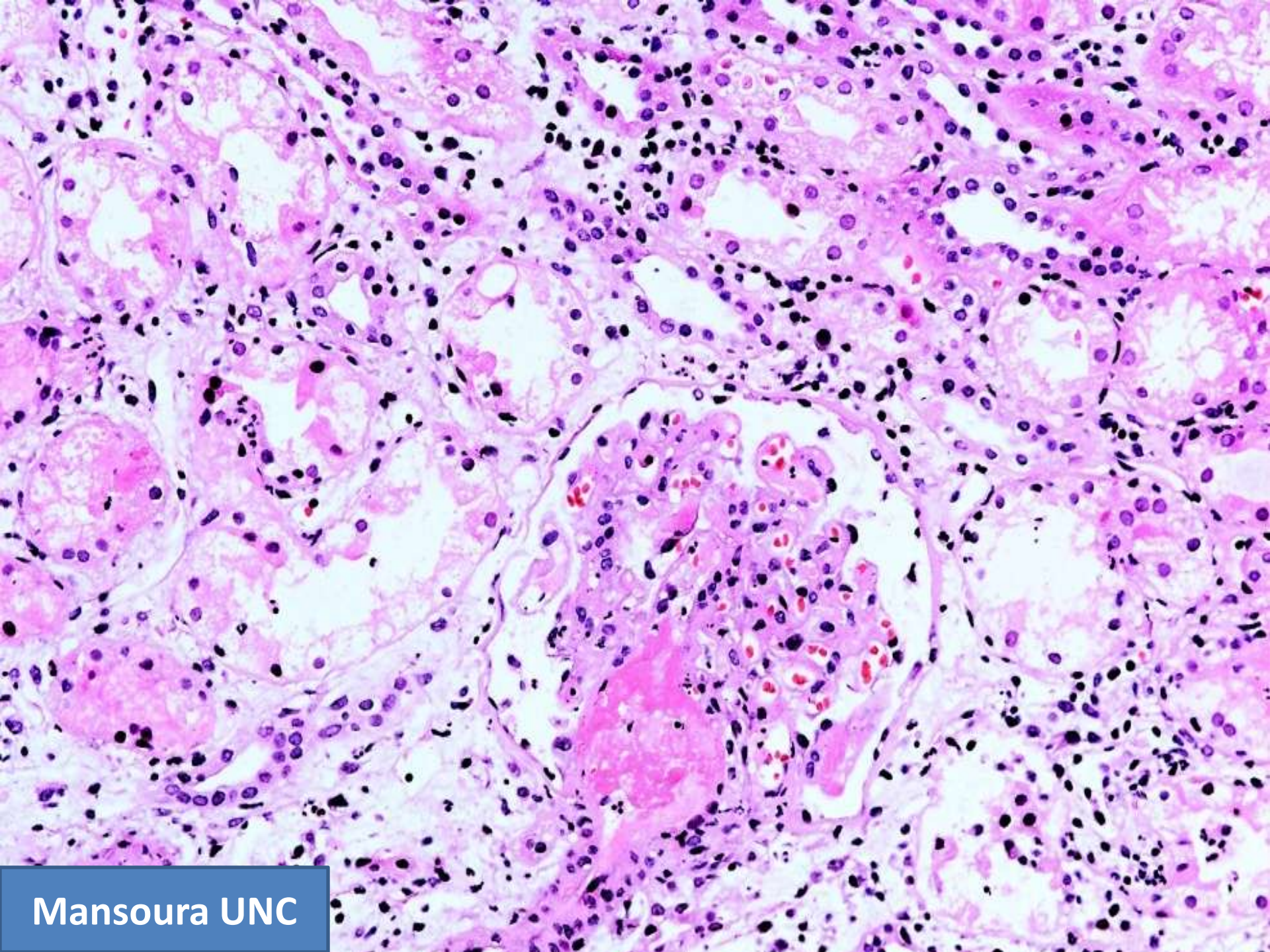
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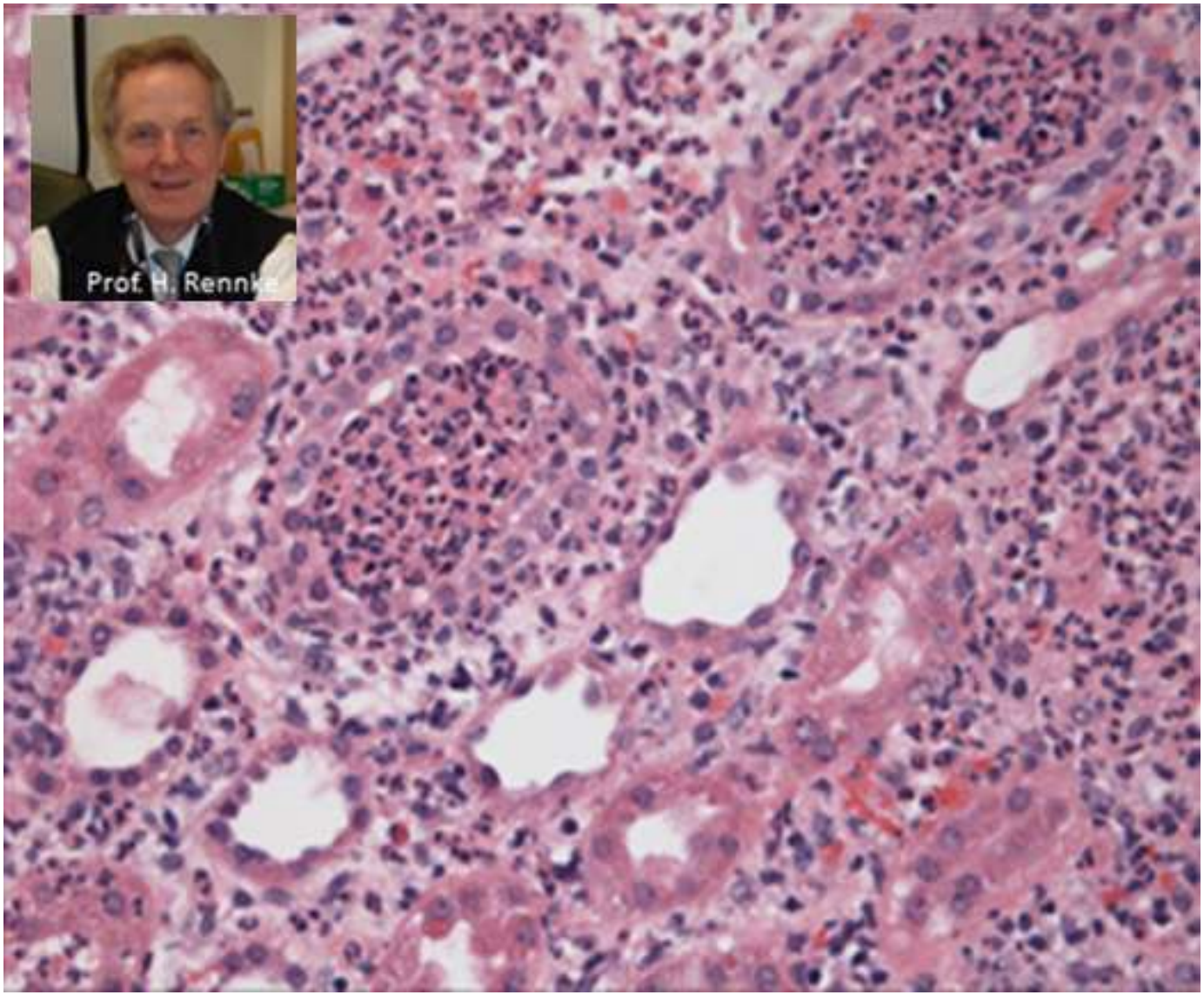
What is The Diagnosis?



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5

Infections

Urinary tract Infection and Renal Transplantation

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REVIEW

CURRENT OPINION

Asymptomatic bacteriuria and urinary tract infections among renal allograft recipients

Ramandeep Singh[a], *Suzanne E. Geerlings*[b], *and Frederike J. Bemelman*[a]

Curr Opin Infect Dis 2015, 28:112–116

Urinary tract Infection and Renal Transplantation

Urology and Nephrology Center

CLINICAL AND TRANSLATIONAL RESEARCH

Independent Risk Factors for Urinary Tract Infection and for Subsequent Bacteremia or Acute Cellular Rejection: A Single-Center Report of 1166 Kidney Allograft Recipients

Untreated UTI is associated with subsequent ACR

Transplantation 2013;96: 732-738

Urinary tract Infection and Renal Transplantation

Tohoku J. Exp. Med., 2015, **236**, 175-183

Early-Onset Graft Pyelonephritis Is Predictive of Long-Term Outcome of Renal Allografts

Dong Ho Shin,[1] Eun Jung Kim,[1] Samuel Lee,[2] Soo Jin Kim[1] and Jieun Oh[1,3]

[1]Department of Internal Medicine, Kangdong Sacred Heart Hospital, Hallym University, Seoul, Korea
[2]Department of Surgery, Kangdong Sacred Heart Hospital, Hallym University, Seoul, Korea
[3]Department of Internal Medicine, Kangdong Sacred Heart Hospital, Hallym Kidney Research Institute, Hallym University, Seoul, Korea

Urinary tract Infection and Renal Transplantation

Case report

Extensive emphysematous pyelonephritis in a renal allograft: case report and review of literature

EPN of renal allograft according to Al-Geizawi et al.

Stage 1	Gas in the collecting system
Stage 2	Gas replacing <50% of renal parenchyma, with minimum spread to the surrounding tissues. Sepsis rapidly controlled
Stage 3	Gas replacing >50% of renal parenchyma; or extensive spread of infection in the perinephric area; or patient with evidence of multiple organ failure, uncontrolled sepsis, or shock not responding to medical management

EPN, emphysematous pyelonephritis.

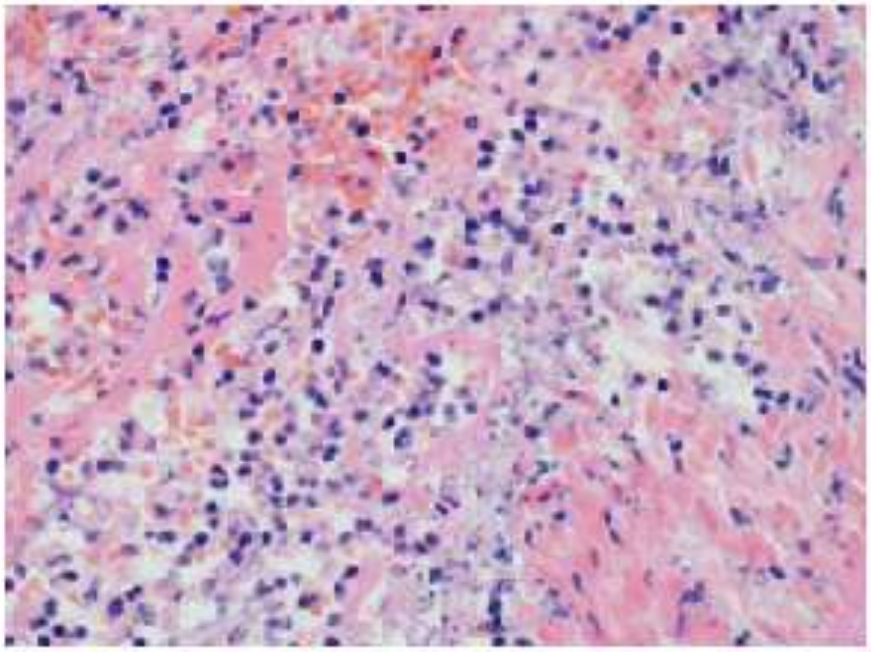
23 patients

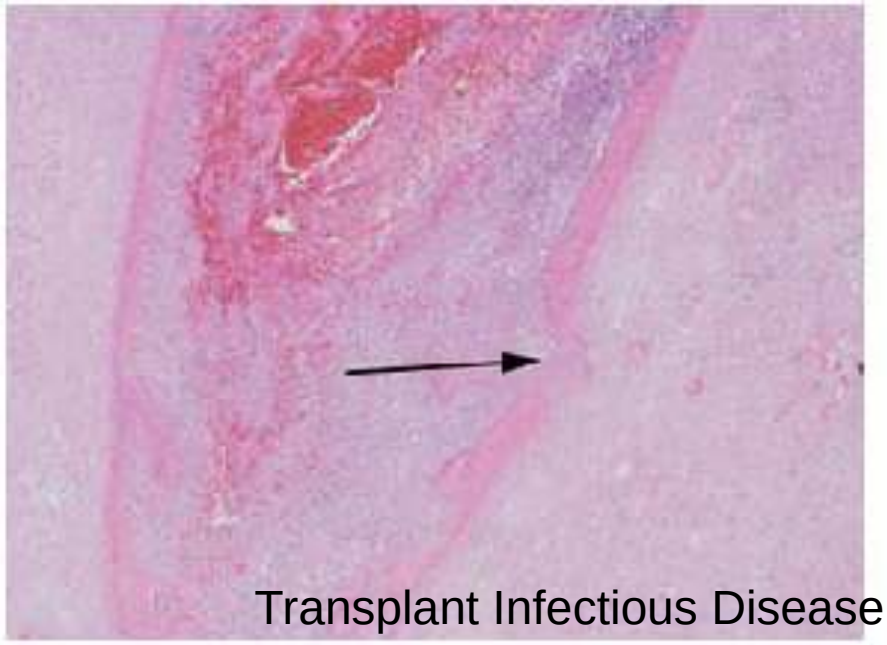
12 graft nephrectomy

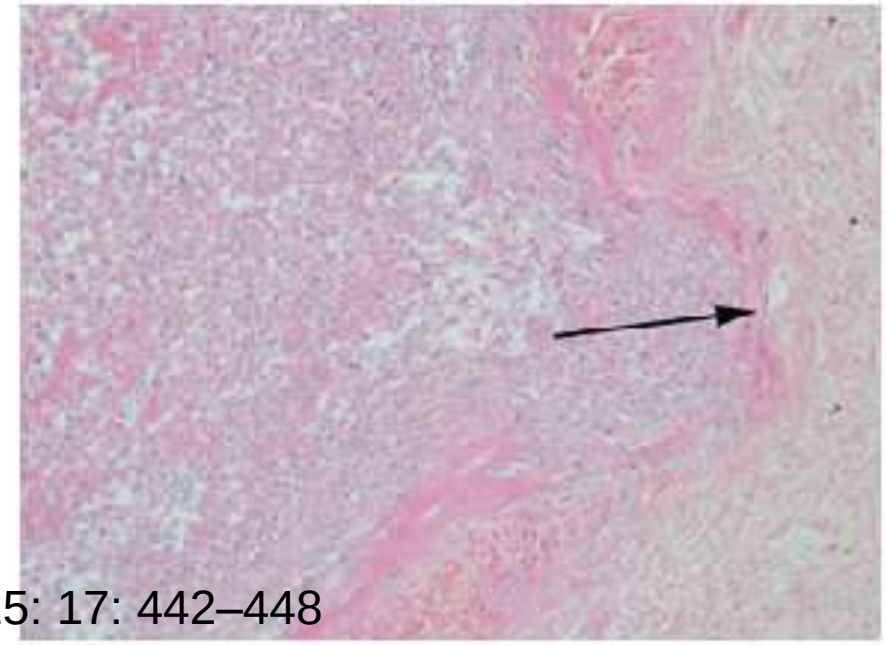
7 graft PCD

4 antibiotics

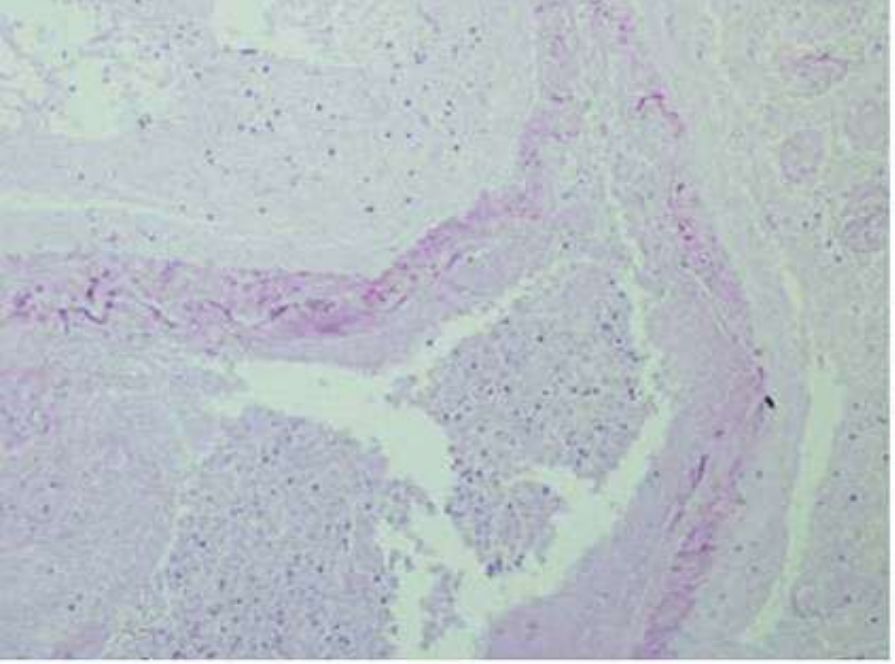
Transplant Infectious Disease 2014: 16: 642–647

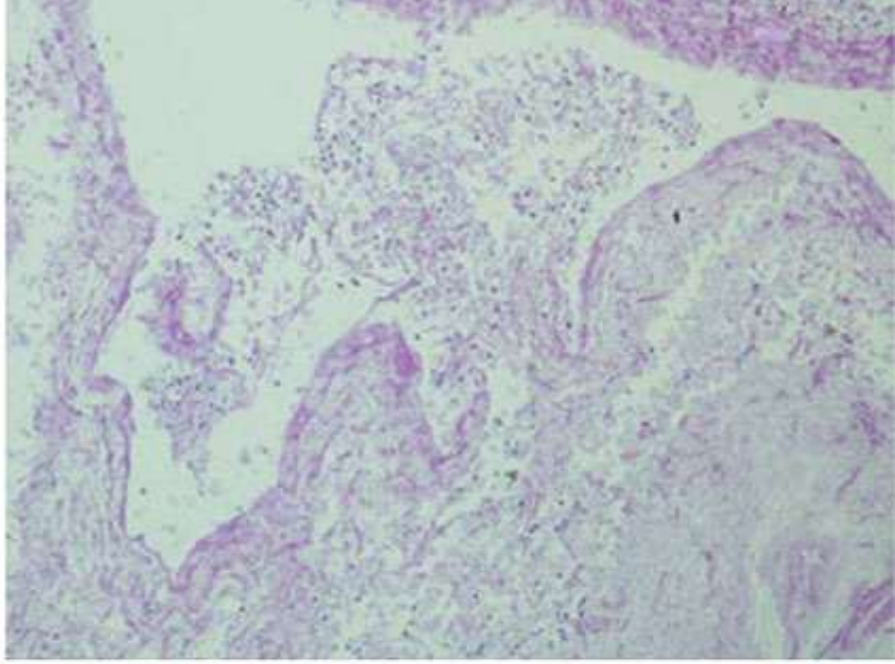


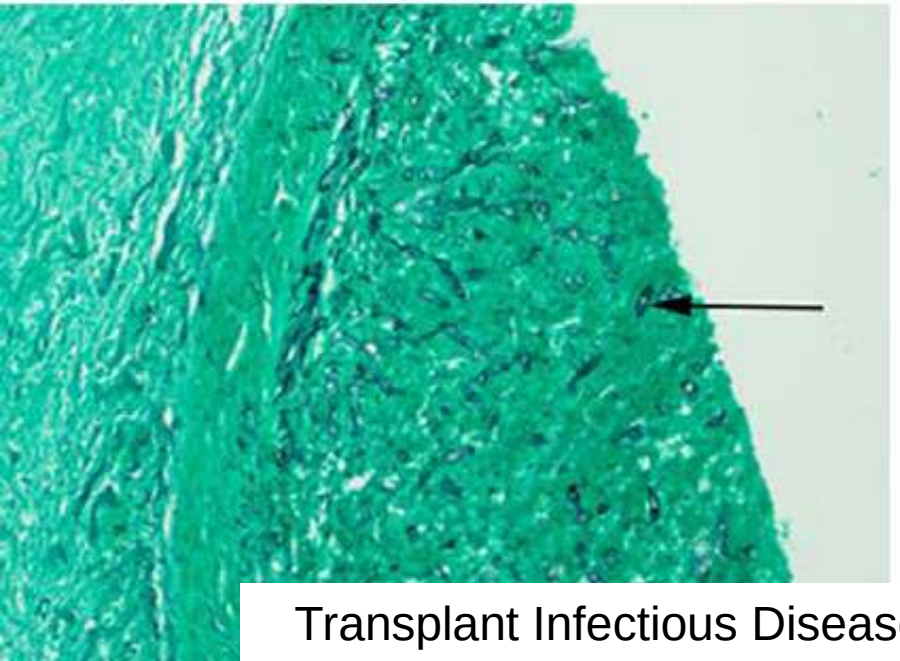


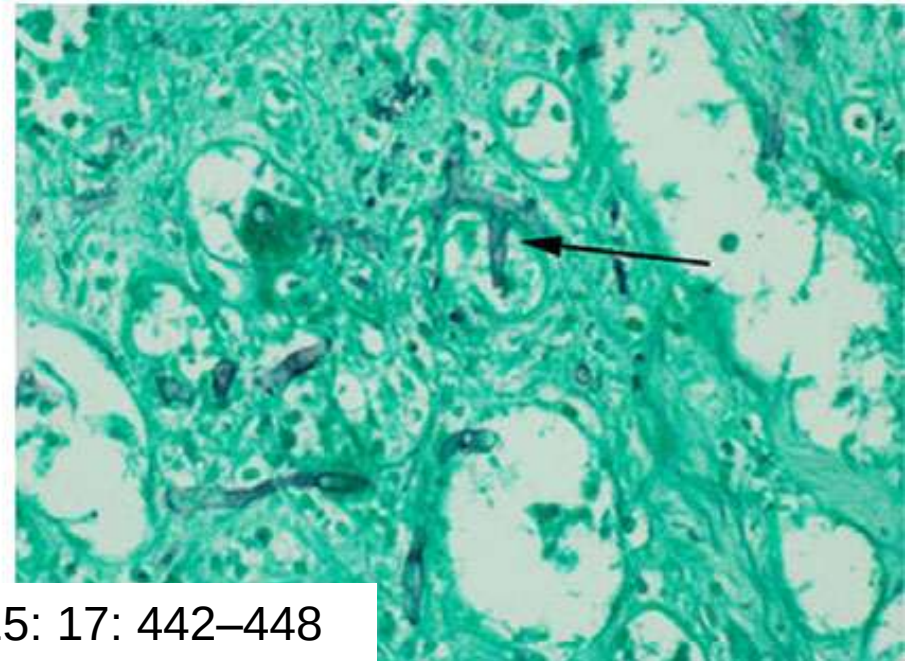


Transplant Infectious Disease 2015: 17: 442–448









Transplant Infectious Disease 2015: 17: 442–448

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Graft Rupture

Graft Rupture

Favi *et al. BMC Urology* (2015) 15:114
DOI 10.1186/s12894-015-0109-3

BMC Urology

CASE REPORT Open Access

CrossMark

Spontaneous renal allograft rupture complicated by urinary leakage: case report and review of the literature

Evaldo Favi[1*], Samuele Iesari[2], Alessandro Cina[3] and Franco Citterio[4]

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Acute Phosphate Nephropathy

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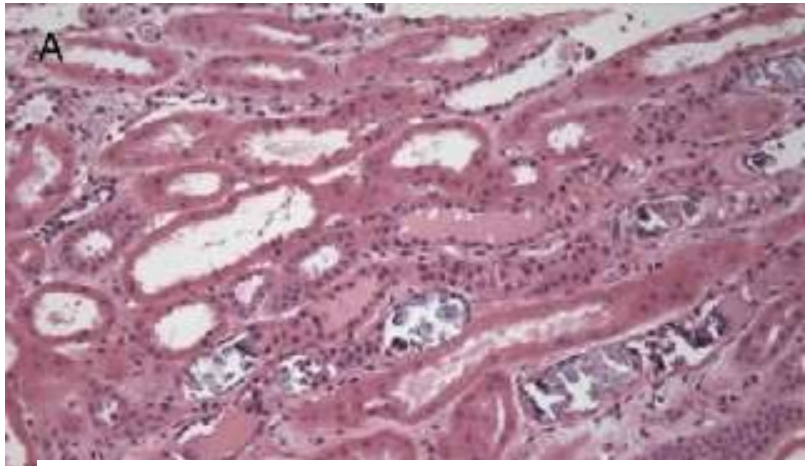

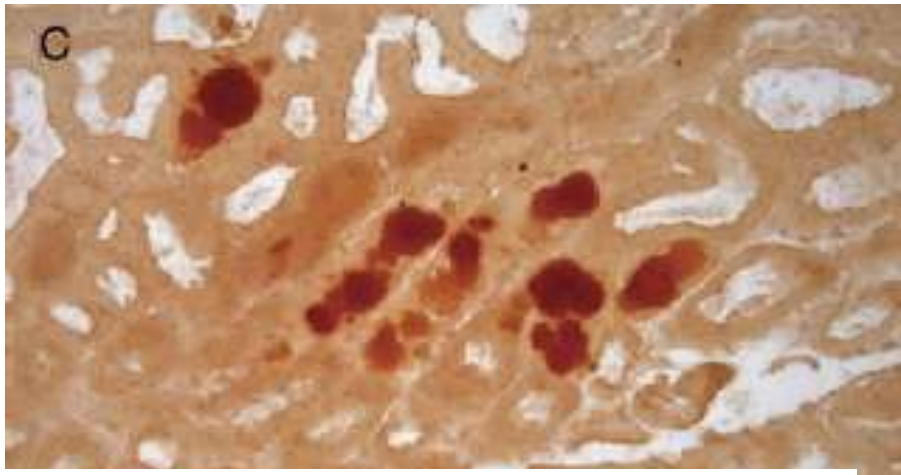

AJKD

Kidney Biopsy Teaching Case

Hypophosphatemia in Kidney Transplant Recipients: Report of Acute Phosphate Nephropathy as a Complication of Therapy

Leonardo V. Riella, MD,[1] Helmut G. Rennke, MD,[2] Monica Grafals, MD,[1] and Anil Chandraker, MD[1]

Am J Kidney Dis. 2011;57(4):641-645

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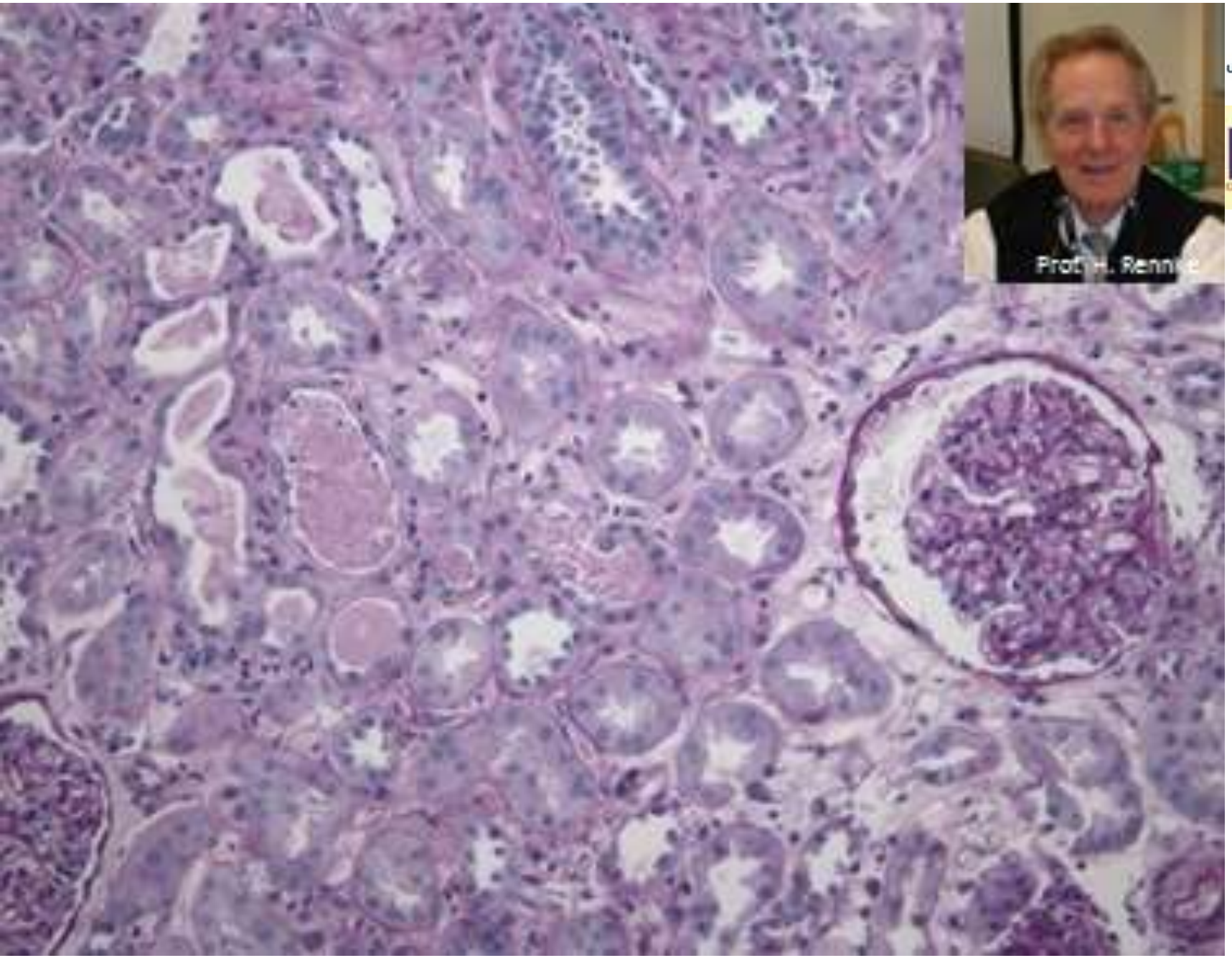
Pre-renal and Intrinsic Causes



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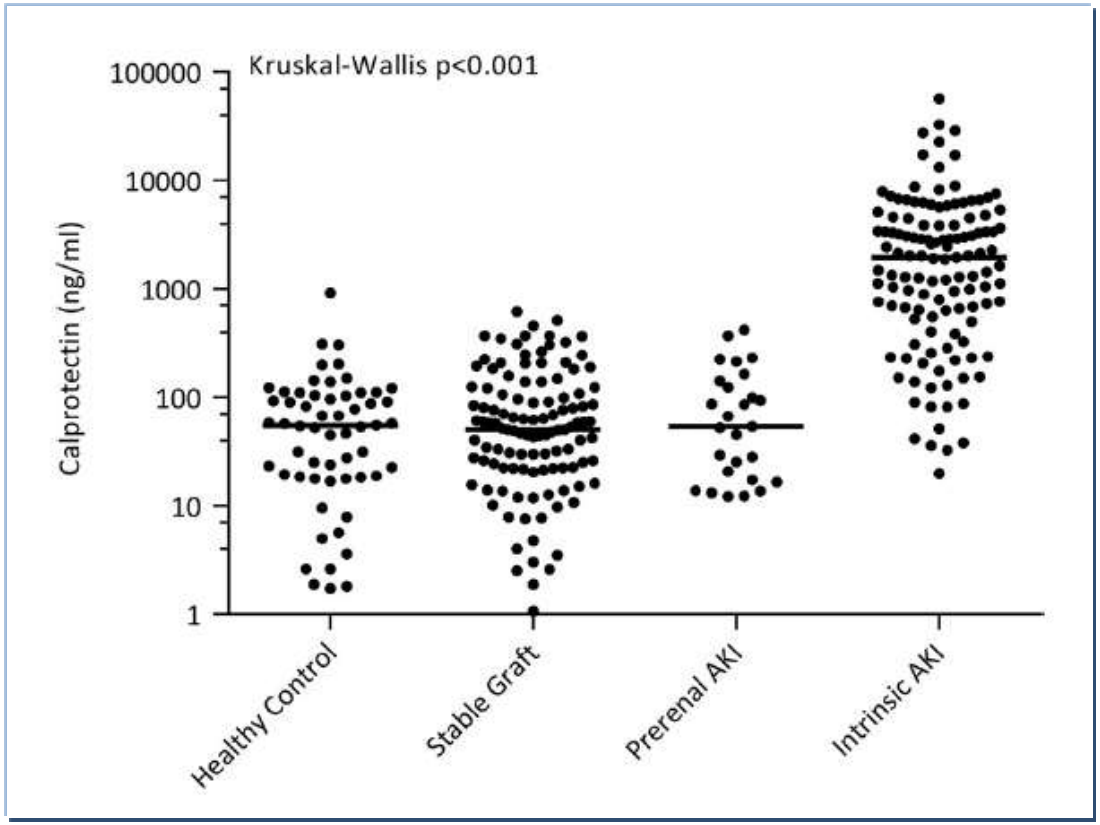
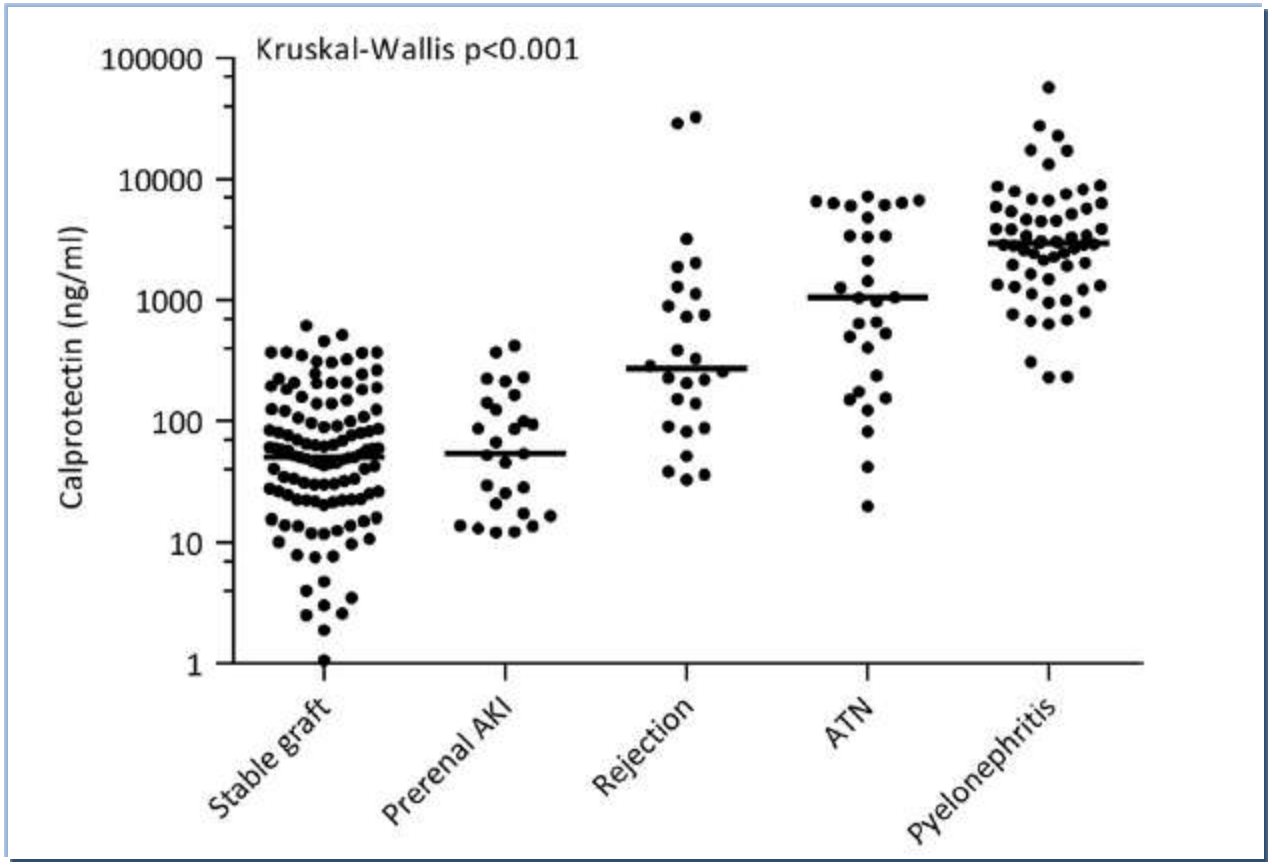
Kidney Injury:
Novel Urinary Biomarker



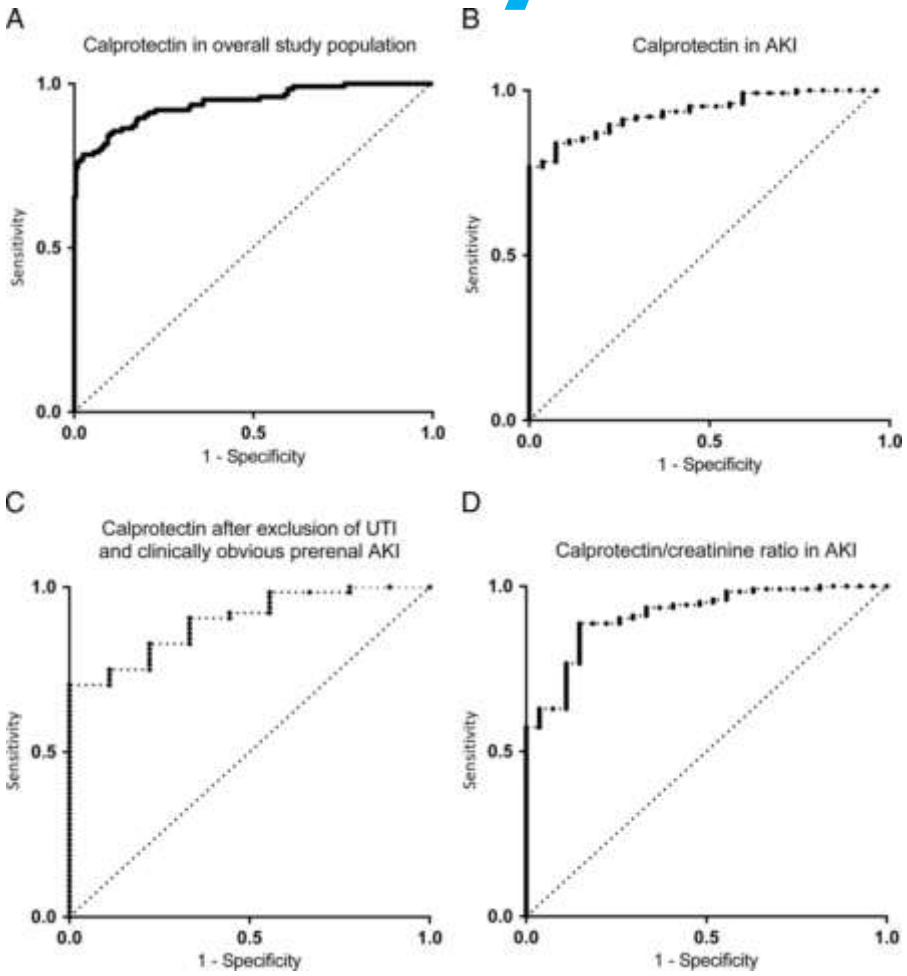
Transplantation 2016;in press

Kidney Injury:
Novel Urinary Biomarker



Transplantation 2016;in press

Kidney Injury:
Novel Urinary Biomarker



Transplantation 2016;in press

Kidney Injury:
Novel Urinary Biomarker

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Original Clinical Science

Urinary Calprotectin Differentiates Between Prerenal and Intrinsic Acute Renal Allograft Failure

Felix S. Seibert, MD,[1,2] Christian Rosenberger, MD,[3] Susanne Mathia, MD,[3] Robert Arndt, MD,[2] Wolfgang Arns, MD,[4] Huppertz Andrea, MD,[4] Nikolaos Pagonas, MD,[1,2] Frederic Bauer, MD,[1,2] Walter Zidek, MD,[2] and Timm H. Westhoff, MD[1,2]

Transplantation 2016;in press

Acute Allograft Dysfunction

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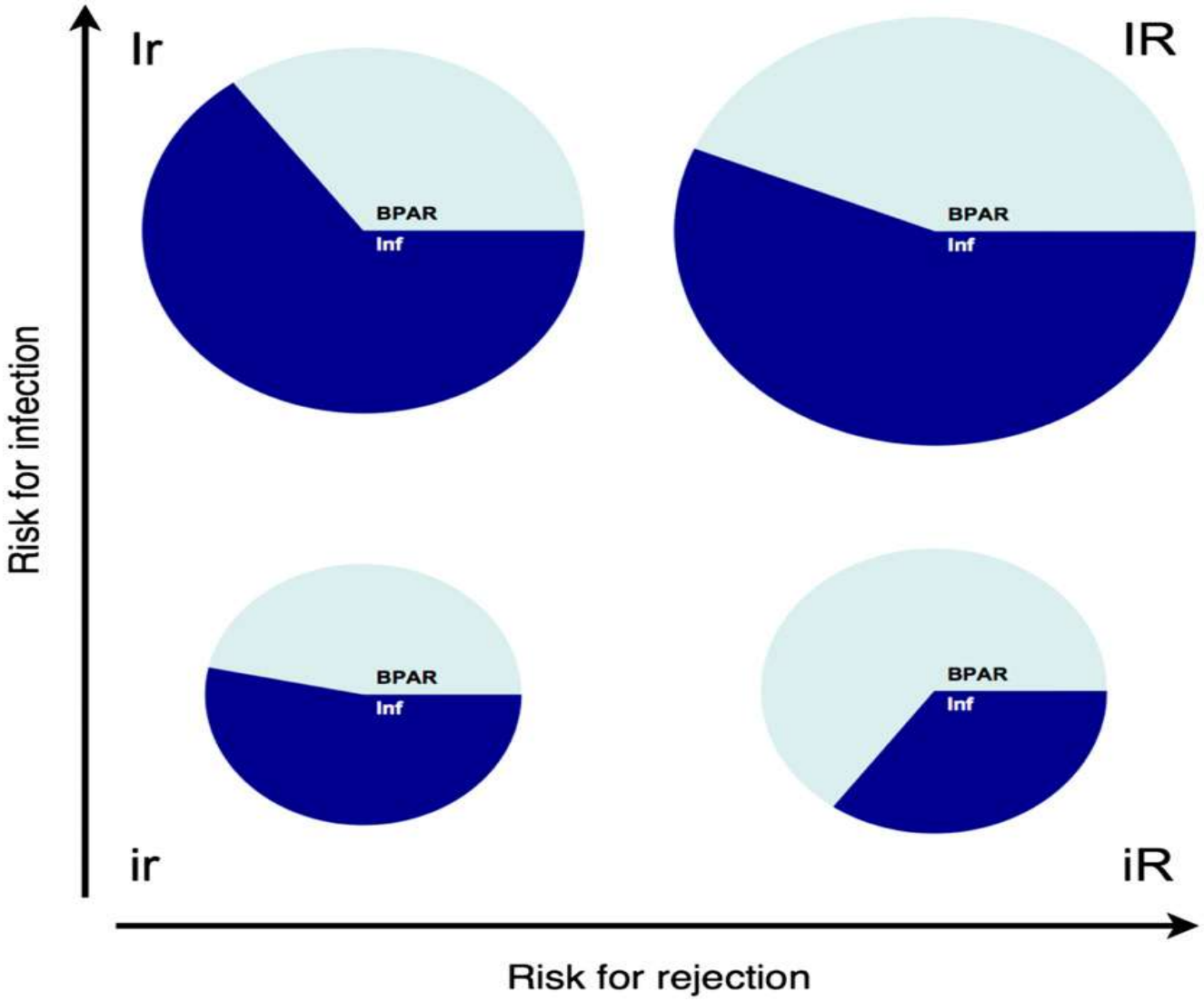
1. Introduction
2. Acute cellular rejection
3. Acute antibody mediated rejection
4. Warm ischemia
5. CNI nephrotoxicity
6. Infection
7. Graft rupture
8. Pre-renal and intrinsic renal
9. Closure



Article

Clin J Am Soc Nephrol 10: 2213–2220, 2015.

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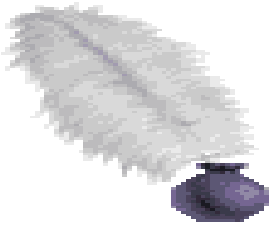

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